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# TUBERCULOUS ANEURYSM OF THE ABDOMINAL AORTA

## REPORT OF A CASE

JAMES N. OWENS JR., M.D., AND ALLAN D. BASS, M.D.

NASHVILLE, TENN.

Tuberculous aneurysm of the abdominal aorta is exceedingly uncommon. Twenty cases were collected by Gellerstedt and Säfwenberg in 1933,[1] at which time they added 1 case of their own. In none of these 21 cases was the abdominal aneurysm due to a blood-borne infection, but it resulted from erosion of the aorta by a tuberculous process in an adjacent lymph node. In only 2 of these cases were tubercle bacilli found in the media of the aorta.[2]

This case report is presented as an instance of (1) a tuberculous aneurysm of the aorta which was not associated with adjacent caseous nodes and (2) an aneurysm in which acid-fast bacilli were demonstrated in the media of the vessel wall.

*History.*—This was the first admission to Vanderbilt University Hospital of a 72 year old white housewife, who entered on Oct. 12, 1943, with the chief complaint of "abdominal pain." Intermittent constipation had been present for over twenty years, and at times when clearing her throat she brought up a few flecks of blood-tinged sputum. Otherwise she had been in excellent health until twenty-three days before admission, at which time she became more constipated, anorexia developed and she experienced a mild generalized upper abdominal pain. Constipation continued to be a prominent symptom. The abdominal pain was present intermittently until the time of admission, being more pronounced on the right side. At times this pain radiated to the right shoulder and the right clavicle. No relationship of the pain to any bodily functions was noted. Afternoon fever, with temperature as high as 104 F., and chills were noted at irregular intervals, and there were days when she was entirely free of fever. During the course of this illness she had lost 25 pounds (11.3 Kg.) in weight.

There was no past or family history of tuberculosis.

*Physical Examination.*—The temperature was 98.2 F., the pulse rate 112, the respiratory rate 24, the weight 101 pounds (45.8 Kg.) and the height 60 inches (152 cm.).

The physical examination at the time of admission revealed a poorly nourished, well developed, alert, cooperative woman of about the stated age. The skin was not remarkable except for evidence of loss of weight. There was no significant enlargement of lymph nodes. There was no tenderness to pressure of the frontal or maxillary sinuses. The ocular fundi revealed moderate tortuosity of the arteries, with arteriovenous nicking. The nose and mouth showed nothing of significance. The thyroid gland was not palpable. The trachea was felt in the midline without tug. An examination of the heart and lungs revealed nothing significant. The blood pressure was 99 systolic and 66 diastolic. There was a thready pulse, but the walls of the radial vessels were not thickened. The abdomen was moderately distended; the liver and spleen were not palpable, and no spasm of the abdominal muscles was noted. A large, moderately tender, firm, slightly movable smooth mass was present in the right lateral portion of the abdomen. The genital and rectal examinations revealed nothing significant. The deep reflexes were physiologically active. The extremities showed no gross deformity or limitation of motion.

*Laboratory Data.*—Blood: The red cell count was 4,470,000, the white cell count 16,650 and the hemoglobin content 14.2 Gm. The differential count showed: polymorphonuclear neutrophils, 93 per cent (segmented), 1 per cent juvenile forms, 2 per cent stab cells and 5 per cent lymphocytes. The platelets were normal, the packed cell volume 42, the sedimentation rate 48.5 and the Kahn reaction negative.

Urine: The specific gravity was 1.018 and the reaction to litmus was neutral. There were a few white blood cells per high power field, no sediment, no red blood cells and a trace of albumin, and the reaction for sugar was negative.

Stool: There was no blood and no parasites.

*Course in the Hospital.*—Because of a falling blood pressure, a rapid thready pulse and the development of cold sweaty hands and feet, a transfusion with 500 cc. of blood plasma followed by 500 cc. of isotonic solution of sodium chloride was given a few hours after her admission to the hospital. The blood pressure rose from 85 systolic and 55 diastolic to 140 systolic and 70 diastolic associated with definite subjective improvement. A barium sulfate enema showed displacement of the viscera of the right upper quadrant medially and inferiorly and obliteration of the right psoas line with slight scoliosis to the left. A retrograde pyelogram showed a slight dilatation of the right renal pelvis with

From the Department of Pathology and the Department of Medicine, Vanderbilt University School of Medicine.

1. Gellerstedt, N., and Säfwenberg, O.: Zur Kenntnis der Aortatuberkulose und des tuberkulösen Arrosionsaneurysmas der Aorta, Upsala läkaref. förh. **38**:165-181, 1933.

2. Dafoe, W. A.: Ruptured Aneurysms of Abdominal Aorta Due to Tuberculosis, Edinburgh M. J. **32**:291-296 (June) 1925.

enlargement of the right kidney. At cystoscopic examination no indigo carmine dye came from the right ureter. Urine obtained from the right kidney showed an occasional white blood cell; otherwise the urine from both kidneys was normal. Her temperature went to 102 and 103 F. on the second and third hospital days respectively. The pulse remained rapid, at 100 to 120 per minute. The pain in the right flank was severe and constantly present and was only partially relieved by opiate analgesia.

On October 15, at 4 p. m., the blood pressure was 100 systolic and 65 diastolic, the pulse rate 96, the red blood cell count 2,000,000 and the hemoglobin content 6 Gm. A determination of the nonprotein nitrogen level performed at this time gave a value of 39 mg. per

*A*, the arrow points to the rent in the right anterior wall of the abdominal aorta. Note the large perirenal hematoma which is present in the lower left portion of the photograph. *B*, transverse section of the aorta at the site of rupture, showing the small false aneurysmal sac and the large laminated blood clot.

hundred cubic centimeters. Because of the falling blood pressure and the evidence of loss of blood, 500 cc. of citrated whole blood was given, bringing the blood pressure up to 133 systolic and 90 diastolic. At 7 p. m. the blood pressure had again fallen, this time to 82 systolic and 52 diastolic, and there was a decided increase in the size of the mass in the right upper quadrant. No free fluid could be detected in the abdomen. Death occurred at 7:30 p. m. on the fourth hospital day.

*Necropsy.*—Gross Observations: The autopsy was performed one and a half hours after death on the body of a fairly well developed but poorly nourished white woman. There were no gross abnormalities of the head, eyes, ears, nose, mouth, neck or thorax. The abdomen was symmetrically distended. A rather soft mass was felt in the right lateral portion of the abdomen extending almost to the umbilicus. It was freely movable but returned to its original position when released.

A small amount of blood-tinged fluid was seen in the peritoneal cavity when the abdomen was opened.

In the right paravertebral gutter was a large perirenal hematoma, which had displaced the viscera medially. The liver was separated from the upper margin of the mass by a reflection of the peritoneum. The cecum and the ascending colon were displaced anteriorly and were incorporated in the anterior portion of the hematoma. The psoas muscle on the right was not identifiable. There was extension of hemorrhage from the lower border of the hematoma into the right parametrium. Attached to the mediocephalad vertebral surface of the hematoma was a small firm brownish purple dumb-bell-shaped mass, measuring 8 by 6 cm., which encircled the anterior margin of the abdominal aorta between the diaphragm and the celiac axis.

The pleural cavities were not revealing, save for the presence of a few fibrous adhesions at the posterior portions of the lower lobes of the lungs. The pericardial sac was not remarkable. The heart weighed 350 Gm. The myocardium was brownish red, rather firm and of normal thickness. The endocardium and valves were normal. The coronary arteries were felt as rather firm cords, but the lumens were patent. The aorta was incised from the dorsal surface, and an oblong rent 1 cm. in diameter in the wall, with its axis parallel to the aorta, was exposed. This rent was in the right ventral aspect of the aortic wall cephalad to the celiac axis (fig. *A*). The remainder of the aorta was smooth,

with raised yellow plaques which were especially prominent in its abdominal portion. Transverse section made through the small firm mass at the level of the rent showed the edges of the aortic wall to be everted sharply and to end rather abruptly, giving the appearance of a tear in the aorta (fig. *B*). There was lamination of the contained clot, but no true aneurysmal sac was seen. The peritoneal portion of this dumbbell-shaped sac consisted of periaortic connective tissue. There was an oval-shaped laceration measuring 4 by 2 cm. in its largest diameter from this sac into the perirenal space. The aorta and hematoma about the right adrenal and kidney, removed *in toto*, weighed 3,050 Gm. The kidney occupied the most caudal position in the hematoma. The right renal artery ran obliquely downward, and the consequent stretching constricted its lumen close to the orifice. The intima appeared normal where exposed, and no thrombus was found. The celiac axis and superior mesenteric arteries were displaced downward but were patent. No lymph nodes could be found in close proximity to that portion of the aorta between the diaphragm and the celiac axis.

The right and left lungs weighed 350 and 250 Gm. respectively. Numerous small opaque white nodules, 1 2 mm. in diameter, were scattered uniformly throughout the parenchyma of the lungs. These had a slightly yellow, soft, central portion surrounded by a rim of black tissue. There was moderate anthracosis. A large, right hilar node, 2.5 cm. in diameter, was found. The periphery of this node consisted of a thin zone of fibrous tissue, while the central portion was made up of dense gray homogeneous material in which several calcified particles were felt.

There was a diverticulum of the first portion of the jejunum, but otherwise the gastrointestinal tract was not remarkable. The liver weighed 1,530 Gm., and numerous tubercles were found on the cut surface as well as beneath the capsule. The spleen weighed 190 Gm., and several tubercles were found. The pancreas and the adrenals were not remarkable. Numerous tubercles were seen beneath the capsule and on the cut surfaces of both kidneys. There was a stricture of the right ureter at the ureteropelvic junction with dilatation of the pelvis of the kidney. The urinary bladder and the internal genitalia presented no abnormalities.

Microscopic Observations: The aorta showed slight proliferation of the intima. The media did not appear remarkable. The vasa vasorum were normally distributed. The adventitia appeared slightly thickened. At the mouth of the aneurysm there was considerable necrosis of the media with numerous collections of nuclear dust. The adventitia here was noticeably thickened and showed a few multinuclear cells of the Langhans type with moderate lymphocytic and plasma cell infiltration about the vasa vasorum. Just beneath the adventitia was a layer of hyalinized connective tissue with numerous collections of lymphocytes and plasma cells. There was a rapid transition from the media of the aorta at the site of rupture to the wall of the false aneurysmal sac, which appeared to be fibrin. The blood clot beneath it was laminated, but there was no evidence of organization to be made out.

Numerous focal lesions were found in the lungs, liver, spleen, adrenals and kidneys, characterized by centrally located areas of caseous necrosis and radially arranged epithelioid cells surrounded by collections of lymphocytes and plasma cells. A few multinuclear giant cells of the Langhans type were found. The right hilar node showed large areas of caseous necrosis in which spicules of calcium were seen, surrounded by a comparatively thin zone of hyalinized connective tissue. There were a few radially arranged epithelioid cells, collections of lymphocytes and plasma cells. A few multinuclear giant cells of Langhans type were encountered. A section of the bone marrow showed a rather large area of fibrosis surrounded by a few lymphocytes and plasma cells and containing several multinuclear giant cells of the Langhans type.

Bacteriologic observations of smears made from the nodules in the lung and kidney showed numerous acid-fast, beaded bacilli. Sections of the mouth of the aneurysm stained by Gabbett's method revealed the presence of beaded, slender, acid-fast bacilli between the elastic tissue fibers of the aorta.

## COMMENT AND CONCLUSIONS

This is the twenty-second reported case of tuberculous aneurysm of the abdominal aorta and to our knowledge the only case of blood-borne infection. In our opinion, acid-fast bacilli were disseminated through the blood stream as a result of the reactivity in a right hilar lymph node. These bacteria were transmitted to the media of the aorta via the vasa vasorum.

# EFFECT OF SODIUM CITRATE ON URANIUM POISONING IN DOGS

G. E. GUSTAFSON, PH.D.; S. KOLETSKY, M.D., AND A. H. FREE, PH.D.
CLEVELAND

Certain substances have been shown to protect the kidneys from injury by heavy metals. Protection from poisoning by uranyl nitrate has been obtained by sodium carbonate,[1] sodium bicarbonate [2] and sodium citrate,[3] and from mercuric chloride, by hemoglobin [4] and testosterone.[5]

This study deals with the protective action of sodium citrate in dogs receiving an otherwise lethal dose of uranyl nitrate.

## METHODS

Twenty female dogs, weighing between 7.7 and 20 Kg. and appearing in good health, were used as experimental animals. Those selected were neither extremely young nor senile. The diet was a commercial preparation of dog biscuits. There was no restriction of intake of water. Intravenously administered sodium pentobarbital was used as the anesthetic in obtaining biopsy specimens.

The uranyl nitrate was given intravenously in every instance. Sodium citrate was given by the oral or intravenous route prior to and after the injection of uranyl nitrate. The intravenous route was used in the early experiments but was changed to oral because of greater ease of administration.

The dogs were studied in pairs, i. e., a control dog which received only uranyl nitrate and a treated dog which received both uranyl nitrate and sodium citrate. The two in a pair were of similar weight and body type. In all, 10 pairs [6] of animals were studied. In 7 pairs the treated animal was given the sodium citrate orally and in 3 pairs intravenously.

In the group in which the treated dogs were given the citrate orally the 7 control dogs received a single intravenous injection of 5 mg. of anhydrous uranyl nitrate per kilogram of body weight in a 0.5 per cent aqueous solution. Injection was made into the jugular vein over a period of approximately two minutes. Six of the other dogs were treated similarly and in addition received doses of 1.15 Gm. of anhydrous sodium citrate per kilogram of body weight given by stomach tube two hours before and immediately after the injection of uranyl nitrate and at twenty-four, forty-eight, seventy-two and ninety-six hours thereafter. One dog received 2.3 Gm. of anhydrous sodium citrate per kilogram of body weight daily for five days preceding and five days following the injection of uranyl nitrate.

Three pairs of dogs were used to observe the effect of intravenous administration of sodium citrate on uranium poisoning. The method employed was similar to that of Donnelly and Holman.[3] All 6 dogs received a single intravenous injection of 5 mg. of anhydrous uranyl nitrate per kilogram of body weight. Three of the 6 animals also received 230 mg. of anhydrous sodium citrate per kilogram of body weight in a 1 per cent aqueous solution on each of five days preceding and five days following the administration of the uranyl nitrate. The citrate was injected by the intravenous drip method into either the jugular or the femoral vein over a period of one-half to one hour.

The blood urea nitrogen, serum carbon dioxide and serum chlorides were determined daily, the creatinine level every fourth day and the urea clearance (maximal clearance) on alternate days or every fourth day. A terminal determination of creatinine was also made. Studies of urea clearance obviously could not be carried out after anuria was established. Control studies of the blood and of the urea clearance were performed on every dog on two separate days before the experiment was begun.

From the Department of Biochemistry and the Institute of Pathology, School of Medicine, Western Reserve University.

Drs. William Abbott and Maynard Pride, Department of Surgery, Western Reserve University, assisted us in obtaining the biopsy specimens from the kidneys.

The data presented in this paper are taken from the dissertation submitted by G. E. Gustafson to the Graduate School of Western Reserve University, June 1943, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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3. Donnelly, G. L., and Holman, R. L.: The Stimulating Influence of Sodium Citrate on Cellular Regeneration and Repair in the Kidney Injured by Uranium Nitrate, J. Pharmacol. & Exper. Therap. **75**:11 (May) 1942.

4. Havill, W. H.; Lichty, J. A., Jr., and Whipple, G. H.: Tolerance for Mercury Poisoning Increased by Frequent Hemoglobin Injections, J. Exper. Med. **55**: 627 (April) 1932.

5. (*a*) Selye, H.: On the Protective Action of Testosterone Against the Kidney Damaging Effect of Sublimate, J. Pharmacol. & Exper. Therap. **68**:454 (April) 1940. (*b*) Longley, L. P.: Effect of Treatment with Testosterone Propionate on Mercuric Chloride Poisoning in Rats, ibid. **74**:61 (Jan.) 1942.

6. Two dogs which died of complications unrelated to renal damage were replaced by other animals.

The following methods were used: urea, Van Slyke and Cullen[7]; urea clearance, Möller, McIntosh and Van Slyke[8]; creatinine, Myers[9]; serum chlorides, Wilson and Ball[10]; serum carbon dioxide content, Van Slyke and Neill.[11]

Urine was analyzed for uranium by first evaporating the sample to dryness over a steam bath. The concentrate was then transferred to a hot plate, where most of the nitrogenous material was decomposed. Final ashing was carried out in a furnace, and the ash was then taken up in 5 per cent sulfuric acid. This solution was filtered and uranium determined on the filtrate by the method of Kolthoff and Lingane.[12]

The correction for indicator in this method was determined empirically by working with mixtures of the same composition as the solution to be titrated. In agreement with Kolthoff and Lingane, the correction was found to be 0.15 cc. of hundredth-normal potassium dichromate solution per 0.24 cc. of 0.2 per cent indicator.

Duplicate blank determinations on twenty-four hour samples of urine known to contain no uranium gave extremely small titers, of 0.88 and 0.92 cc. of hundredth-normal potassium dichromate solution. Duplicate determinations for uranium, made after the latter was added to twenty-four hour samples of urine in amounts equivalent to 10 cc. of hundredth-normal potassium dichromate solution, gave recovery values of 97.8 and 99 per cent.

Biopsy of the kidney was performed on some dogs, and autopsies were performed on all animals which died or were killed. After autopsy paraffin sections were prepared routinely from the kidneys and stained with hematoxylin and eosin. Sections were also made of other organs, including the liver, but these are not pertinent to the present problem.

Special stains for uranium were made according to the method of Gérard and Cordier.[13] After deparaffinization the sections were placed in a solution of equal parts of 10 per cent potassium ferrocyanide and 20 per cent hydrochloric acid for twenty minutes. They were then washed in water and counterstained for three minutes in 1 per cent aqueous solution of kernechtrot. The uranium precipitate has a brown color. The method is apparently specific for uranium.

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13. Gérard, P., and Cordier, R.: Etudes histophysiologiques sur le rein des anoures, Arch. de biol. **43**:367, 1932.

## RESULTS

Five of the 10 control dogs died in uremia at intervals ranging from four to ten days after the injection of uranyl nitrate. The 5 other animals were put to death at periods of sixty hours and four, five, six, and seven days respectively after the injection. Biopsy specimens of the kidneys were obtained from 6 different control dogs at intervals of two, eight, twenty-six (2 animals), forty-eight, sixty and seventy-two hours after the injection.

All 7 dogs given sodium citrate orally survived the acute phase of uranium poisoning. They were killed at periods of sixty hours, four, five, six, seven and ten days and five weeks respectively after the injection of uranyl nitrate. Prior to their death biopsy specimens of the kidneys were obtained from 6 of these dogs at periods of two, eight, twenty-six (2 animals), forty-eight, sixty and seventy-two hours after the injection.

TABLE 1.—*Chemical Studies on Ten Control Dogs* * (Given Uranyl Nitrate Only)*

| Sample | Urea Nitrogen, Mg. per 100 Cc. | | | Urea Clearance, C max.† | Blood Creatinine, Mg. per 100 Cc. | Serum Chlorides, mEq. per Liter | Serum $CO_2$ Content, Vol. per 100 Cc. |
|---|---|---|---|---|---|---|---|
| | Average | Minimum | Maximum | | | | |
| Control (1) | 11.8 | 6 | 18 | 39.7 | 1.1 | 103.2 | 48.8 |
| Control (2) | 10.9 | 6 | 15 | 39.3 | 1.0 | 103.9 | 51.8 |
| 1 day | 37.3 | 21 | 58 | .... | ... | 96.2 | 42.0 |
| 2 day | 72.8 | 54 | 107 | 2.8 | ... | 97.3 | 39.0 |
| 3 day | 106 | 71 | 165 | .... | ... | 96.3 | 34.0 |
| 4 day | 137 | 88 | 224 | 0.3 | 9.9 | 94.1 | 31.7 |
| 5 day | 170 | 95 | 231 | Anuria | ... | 88.9 | 25.9 |
| 6 day | 195 | 107 | 272 | Anuria | ... | 91.4 | 22.9 |
| 7 day | 262 | 216 | 361 | Anuria | ... | 88.7 | 24.6 |
| 8 day | 280 | 252 | 294 | Anuria | 21.8 | 85.3 | 19.2 |
| 9 day | 319 | 314 | 353 | Anuria | .... | 73.4 | 22.6 |
| 10 ady | 361 | 322 | 400 | Anuria | 25.8 | 61.2 | 32.5 |

* Figures for each day represent average values for all dogs.
† Number of cubic centimeters of blood cleared of urea per minute.

All 3 dogs receiving sodium citrate intravenously survived. One animal was killed on the ninth day after the injection of uranyl nitrate, at the time of the death of its corresponding control. Two dogs were killed on the twenty-first day.

*Chemical Studies of the Blood.*—A summary of the data for the 10 control dogs is shown in table 1. Increase in blood urea nitrogen became manifest as early as the day following the injection. The increase was progressive, and at the time of the animals' death the values ranged from 314 to 400 mg. per hundred cubic centimeters of blood (fig. 1). The animals became anuric by the fourth or fifth day. The level of creatinine was greatly increased by the fourth day and terminally reached values between 21 and 29 mg. per hundred cubic centimeters. Serum chloride levels showed very little change in the early stage of uranyl nitrate poisoning. However, in the terminal phase the values dropped abruptly to

levels between 61.2 and 77.5 milliequivalents per liter of serum. Beginning on the second day acidosis was indicated by reduction of serum carbon dioxide values. These were variable but consistently low.

A summary of the data for the 7 dogs given sodium citrate orally is shown in table 2. It is evident that the functional changes were slight and recovery rapid. The maximum value for blood urea nitrogen ranged from 10 to 60 mg. per hundred cubic centimeters. On the sixth day the urea clearance was reduced to its lowest

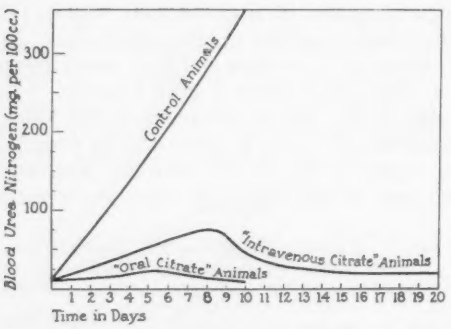
Blood Urea Nitrogen (mg. per 100 cc.)
300
200
100
Control Animals
"Intravenous Citrate" Animals
"Oral Citrate" Animals
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Time in Days

Fig. 1.—Comparison of values for blood urea nitrogen in control and in citrate-treated animals.

level, about one third of the control value. By the tenth day the values for both blood urea nitrogen and urea clearance were normal. There was no significant elevation of creatinine. The serum chloride values were not altered. The serum carbon dioxide content tended to be high during the period of administration of sodium citrate but returned to normal promptly after the administration of the alkali was discontinued.

TABLE 2.—*Chemical Studies on Seven Dogs Given Sodium Citrate Orally* *

| Sample | Urea Nitrogen, Mg. per 100 Cc. Average | Minimum | Maximum | Urea Clearance, C max. | Blood Creatinine, Mg. per 100 Cc. | Serum Chlorides, mEq. per Liter | Serum $CO_2$ Content, Vol. per 100 Cc. |
|---|---|---|---|---|---|---|---|
| Control (1) | 11.4 | 8 | 16 | 43.7 | 1.1 | 106.9 | 50.9 |
| Control (2) | 10.9 | 7 | 14 | 40.5 | 1.1 | 102.8 | 52.4 |
| 1 day | 12.8 | 9 | 20 | .... | ... | 98.1 | 59.5 |
| 2 day | 13.8 | 6 | 21 | 22.4 | ... | 100.2 | 61.5 |
| 3 day | 15.4 | 7 | 22 | .... | ... | 103.7 | 55.8 |
| 4 day | 18.3 | 6 | 34 | 19.1 | 1.6 | 104.9 | 55.9 |
| 5 day | 23.9 | 9 | 60 | .... | ... | 103.5 | 51.1 |
| 6 day | 19.8 | 10 | 57 | 12.9 | ... | 103.6 | 51.0 |
| 7 day | 19.9 | 6 | 32 | .... | ... | 103.8 | 52.8 |
| 8 day | 12.8 | 5 | 19 | 35.9 | 1.1 | 102.7 | 51.6 |
| 9 day | 10.6 | 7 | 13 | .... | ... | 105.5 | 49.2 |
| 10 day | 9.4 | 8 | 10 | 42.4 | 1.2 | 103.3 | 55.6 |

* Figures for each day represent average values for all dogs.

The results for the 3 dogs given sodium citrate intravenously are given in table 3. The maximum value for blood urea nitrogen, ranging from 47 to 96 mg. per hundred cubic centimeters of blood, was reached on the seventh or eighth day, and thereafter the levels declined (fig. 1). The values for 2 dogs on the twenty-first day, when they were killed, were in the upper limit of normal. The average urea clearance was the lowest, 10 per cent of the control figure, on the eighth day, when the blood urea was maximum. Thereafter the values gradually increased to 30 per cent of the control level on the twentieth day. The change in blood creatinine was similar to that in urea nitrogen. There was no significant alteration of serum chlorides. Only a relatively small decrease of serum carbon dioxide occurred in comparison with the control animals. Recovery from this slight acidosis was complete by the twelfth day, and the subsequent values were normal.

*Urinalyses.*—Dextrose and protein were present in the urine collected during the first twenty-four hours after the injection of uranyl nitrate. On a rough quantitative basis, they were found

TABLE 3.—*Chemical Studies on Three Dogs Given Sodium Citrate Intravenously* *

| Sample | Urea Nitrogen, Mg. per 100 Cc. Average | Minimum | Maximum | Urea Clearance, C max. | Blood Creatinine, Mg. per 100 Cc. | Serum Chlorides, mEq. per Liter | Serum $CO_2$ Content, Vol. per 100 Cc. |
|---|---|---|---|---|---|---|---|
| Control (1) | 14.3 | 6 | 10 | 35.4 | 1.1 | 106.8 | 50.6 |
| Control (2) | 15.6 | 8 | 12 | 32.3 | 1.0 | 101.3 | 56.1 |
| 1 day | 21.7 | 10 | 34 | .... | ... | 101.7 | 44.6 |
| 2 day | 27.7 | 14 | 50 | .... | ... | 107.7 | 36.7 |
| 3 day | 33.4 | 22 | 44 | .... | ... | 106.9 | 36.8 |
| 4 day | 41.5 | 27 | 54 | 5.2 | 4.9 | 98.2 | 39.6 |
| 5 day | 50.9 | 39 | 65 | ... | ... | 105.3 | 44.2 |
| 6 day | 57.1 | 42 | 78 | ... | ... | 104.0 | 45.4 |
| 7 day | 71.2 | 47 | 94 | ... | ... | 104.8 | 40.1 |
| 8 day | 76.7 | 44 | 96 | 3.3 | 8.0 | 98.2 | 43.1 |
| 9 day† | 66.8 | 36 | 74 | ... | ... | 105.4 | 40.0 |
| 10 day | 41.0 | 30 | 52 | ... | ... | 105.0 | 50.4 |
| 12 day | 31.4 | 24 | 38 | 5.2 | 4.1 | 102.9 | 53.4 |
| 14 day | 22.0 | 22 | 23 | ... | ... | 106.8 | 54.8 |
| 16 day | 19.2 | 18 | 20 | ... | 1.7 | 96.4 | 57.2 |
| 18 day | 20.0 | 17 | 22 | 8.4 | ... | 103.8 | 57.2 |
| 20 day | 19.1 | 15 | 23 | 104.0 | 1.5 | 92.4 | 54.7 |

* Figures for each day represent average values for all dogs.
† One dog was killed on the 9th day.

in approximately equal amounts in the control dogs and the animals given sodium citrate intravenously. However, in the animals given citrate orally the amounts were distinctly less than in the corresponding controls. Dextrose generally appeared in the urine simultaneously with or before the proteinuria. In a few control animals protein was detected as early as the second hour after the injection of uranyl nitrate. The urine of the dogs given the citrate became normal approximately ten days after the injection. In the control dogs, however, the pathologic findings usually persisted until anuria was established.

*Analysis of Urine for Uranium.*—Analyses for uranium were carried out on the urine of control dogs and of dogs given sodium citrate orally (table 4). In the urine of the 7 control dogs the average amount of uranium excreted during the

first twenty-four hours after the injection of uranyl nitrate was 15 per cent of the total amount given, as compared with 58 per cent for the 7 citrate-treated animals. During the twenty-four to forty-eight hour period the average excretion was 3.5 per cent of the total amount for 6 control dogs and 6.4 per cent for 4 animals given citrate orally. One citrate-treated and 2 control dogs had an almost negligible excretion after the initial twenty-four hour period.

*Microscopic Study.*—In the control dogs degenerative change was present as early as two hours after the injection of uranyl nitrate. Necrosis was observed eight hours after the injection and was well marked and diffuse by the end of the second day. It occurred chiefly in the distal or descending portions of the proximal convoluted tubules, which showed loss of nuclei, desquamation of cells and complete blockage of the lumens by necrotic debris. The lesions in other parts of the nephron were comparatively slight. Glomerular changes were slight and consisted of hyperemia, swelling of endothelial and epithelial cells and the presence of granular material and erythrocytes in the capsular space. Edema and exudation of cells, principally lymphocytes, were observed in interstitial location, usually but not always in the vicinity of necrotic tubules.

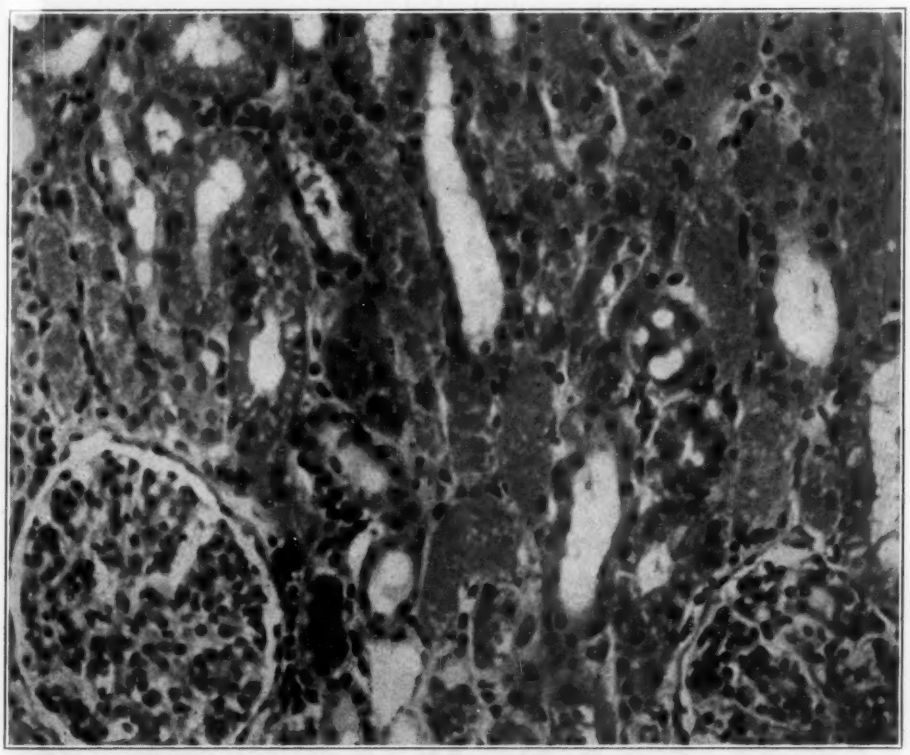

Fig. 2.—Section from a control dog taken sixty hours after the injection of uranyl nitrate (hematoxylin and eosin; × 298). There is diffuse necrosis of renal tubules with blockage of the lumens by necrotic material.

TABLE 4.—*Per Cent of Total Dose of Uranium Excreted in Urine*

| | Control Dogs | | | "Oral Citrate" Dogs | | |
|---|---|---|---|---|---|---|
| Time, Hours | Average | Minimum | Maximum | Average | Minimum | Maximum |
| 0 to 24 | 15.0 | 6.3 | 34.0 | 58.0 | 44.0 | 88.0 |
| 24 to 48 | 3.5 | 0.8 | 7.9 | 6.4 | 0.1 | 17.0 |

Regeneration was present in the control dogs as early as sixty hours after the injection of uranyl nitrate but was usually not well developed until the fifth or sixth day. It occurred mainly in the descending segments of the proximal convoluted tubules. Nuclear repair was prominent and restoration of cytoplasm less marked, slight or even absent. In the later stage of anuria, i. e., in anuric dogs which died or were killed between the sixth and the tenth day, many tubules were still the seat of complete necrosis with little or no regeneration, while others in close proximity showed considerable regeneration or presented widely patent lumens lined by a single layer of flat epithelial cells.

In the dogs given sodium citrate orally the changes in the kidneys were similar to those in the controls up to twenty-six hours after the injection of uranyl nitrate. Thereafter, however, the renal lesions were comparatively slight and consisted merely of focal necrosis of the descending parts of the proximal convoluted tubules. Widespread massive necrosis was not observed in any of the animals. Interstitial exudation of lymphocytes was minimal or absent. There was rapid repair of injured tubular epithelium with complete restoration of both nuclei and cytoplasm. However, in keeping with the slight degree of necrosis, the regenerative change was usually of only slight or moderate intensity. In dogs killed from the sixth to the tenth day after the injection of uranyl nitrate, almost all the descending tubules presented dilated patent lumens lined by flat epithelial cells.

The kidneys of the 2 dogs given sodium citrate intravenously that were killed three weeks after the injection of uranyl nitrate showed no necrosis. The lumens of the descending portions of the proximal convoluted tubules were dilated, patent and lined by a single layer of flat epithelial cells. In the intravenously treated animal killed nine days after the injection, there was necrosis of numerous tubules, but the majority of these were patent, lined by intact healthy epithelium and free of necrotic debris. The regenerative change in this dog was of approximately the same intensity as in the corresponding control animal.

The sections of the kidneys were presented as unknowns to Dr. Howard T. Karsner of the Institute of Pathology, who readily identified those belonging to the control and to the citrate-treated animals in every instance.

*Histochemical Results.*—The kidneys of all but 1 of the control dogs gave a positive reaction for uranium. The brown precipitate, in fine or coarsely nodular form, was found chiefly within the necrotic debris obstructing the lumens of the descending segments of the proximal convoluted tubules. It also occurred in the loops of Henle and in the collecting tubules. The stains were positive in specimens obtained eight hours after the injection of uranyl nitrate and at all periods thereafter, including kidneys from dogs which died in uremia nine or ten days after the injection.

In contrast, only a few of the kidneys of the dogs given sodium citrate orally gave a positive

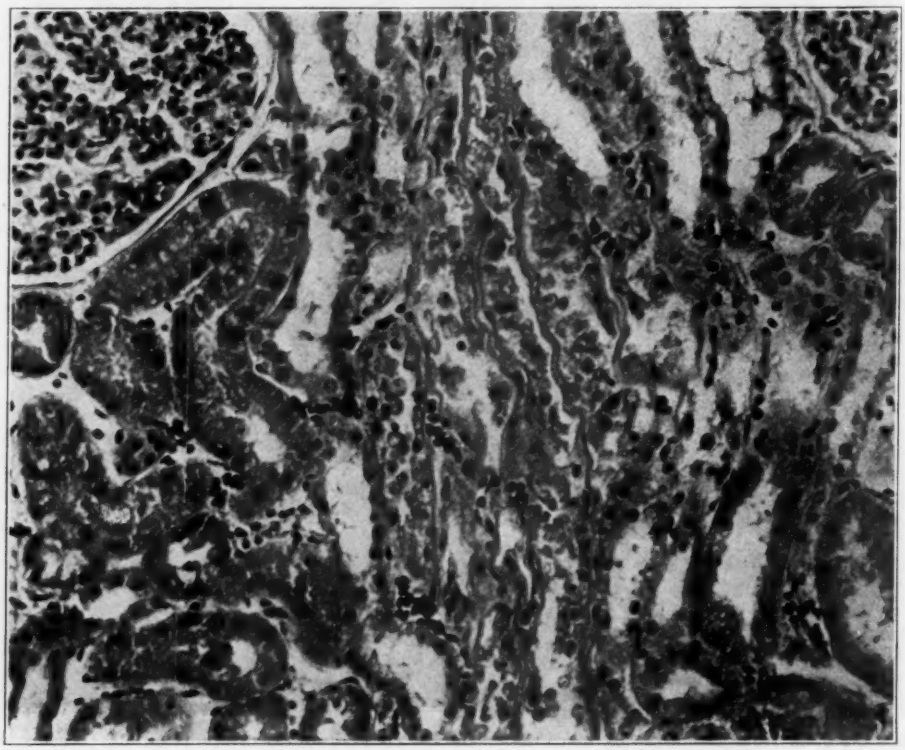

Fig. 3.—Specimen from a dog given sodium citrate orally taken sixty hours after the injection of uranyl nitrate (hematoxylin and eosin: × 298). Necrosis of the epithelium is slight, and the lumens of the tubules are patent.

reaction for uranium. This was less in amount and distribution than in the control dogs. However, in the intravenously treated dog killed on the ninth day after the injection of uranyl nitrate, the amount was comparable to that in the corresponding control animal.

## COMMENT

All the dogs receiving only uranyl nitrate had severe tubular necrosis of the kidneys and died in renal failure. In contrast, the dogs receiving both uranyl nitrate and sodium citrate, either by the oral or by the intravenous route, survived the uranium poisoning.

When given orally the sodium citrate afforded considerable protection against the uranyl nitrate. Functional change in the kidneys, as indicated by chemical studies of the blood, determinations of urea clearance and urinalyses, was comparatively slight, and recovery was rapid and complete. Morphologically the renal lesions were slight, consisting merely of focal tubular necrosis, as compared with the widespread necrosis of the control animals.

Renal damage was greater in the dogs given sodium citrate intravenously than in those treated orally. Renal excretory function was reduced considerably. Retention of blood urea was maximum about the eighth day after the injection of uranyl nitrate and then declined. The rise was more gradual than in the control dogs, and the levels were not as high. In a dog killed on the ninth day after the injection there was considerable necrosis of the renal tubules. However, the lesion was not as extensive as in the control animals and there was a larger number of patent tubules.

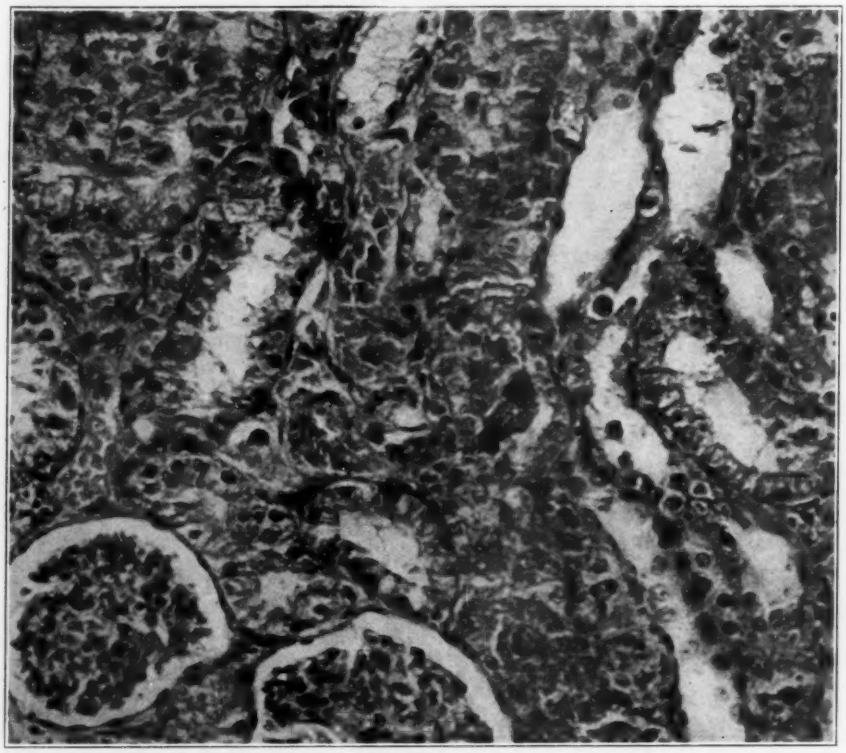

Fig. 4.—Section from a control dog taken six days after the injection of uranyl nitrate (hematoxylin and eosin; × 298). Some tubules are the seat of necrosis, while others show regeneration or have patent lumens lined by flat epithelium.

The greater protection afforded by sodium citrate when given by the oral route is probably explained by the factor of dosage. The dogs given sodium citrate orally received a much larger quantity than those into which it was injected intravenously.

Recently, Donnelly and Holman [8] reported that dogs receiving intravenous injections of sodium citrate survived a lethal dose of uranyl nitrate. The renal damage in such dogs was comparable to that in control animals receiving only uranyl nitrate but was followed by repair, whereas the

controls showed lack of repair. Thus, the beneficial effect of the citrate was attributed to stimulation of regeneration of injured renal epithelium.

In this study the number of dogs given sodium citrate intravenously is too few for analysis. However, the conclusions of Donnelly and Holman do not apply to the dogs receiving sodium citrate orally. In these dogs the renal damage produced by uranyl nitrate was distinctly less severe than in the control animals. As a result, even though the intensity of regenerative change might not be marked, the repair proceeded rapidly to complete restoration of both nuclei and cytoplasm. The control dogs showed considerable regeneration, with reopening of some of the renal tubules, but the repair was incomplete and failed to restore function because of the severity and diffuse nature of the necrosis.

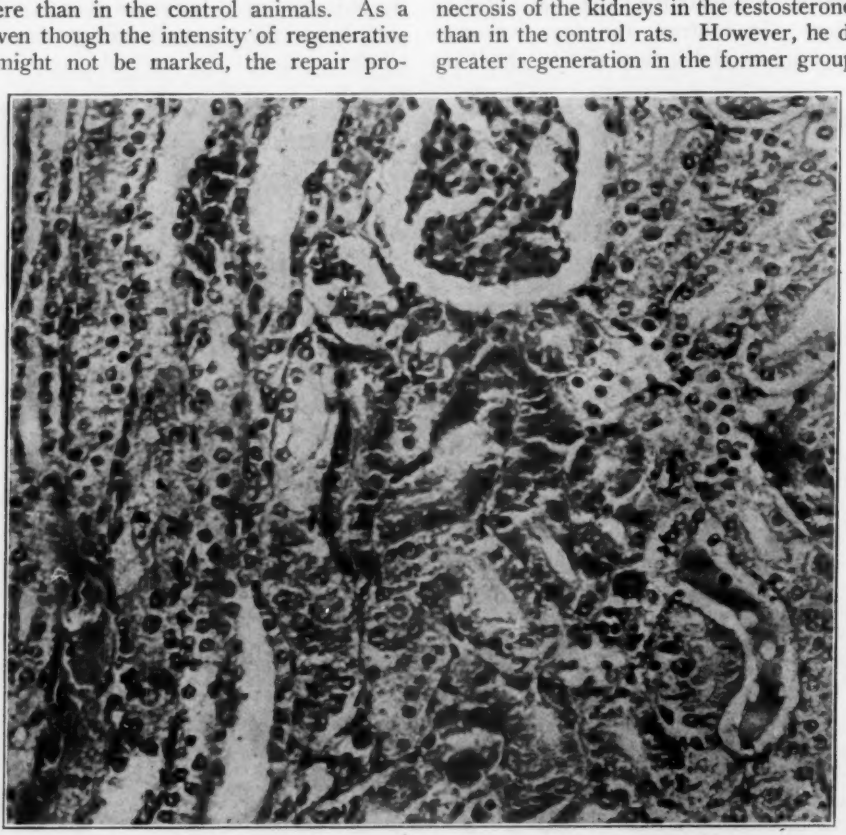

Fig. 5.—Section from a dog given sodium citrate orally taken six days after the injection of uranyl nitrate (hematoxylin and eosin; × 298). There is slight necrosis, but most of the tubules are patent and lined by intact epithelium.

Other substances which protect the kidneys from poisoning by heavy metals have been shown to diminish renal damage. MacNider,[1] who used sodium carbonate, given intravenously, to protect dogs against uranium poisoning, stated that this diminished the severity of the morphologic change in the kidneys. Goto [2] reported similar results with the use of orally administered sodium bicarbonate. Havill, Lichty and Whipple [4] observed that dogs given frequent injections of hemoglobin intravenously can survive otherwise lethal intravenous doses of mercury bichloride with little renal injury. In Selye's [5a] experiments renal necrosis was almost entirely absent in mice protected against subcutaneous injections of mercury bichloride by testosterone. In similar work on rats Longley [5b] found less tubular necrosis of the kidneys in the testosterone-treated than in the control rats. However, he described greater regeneration in the former group.

In this study the uranyl nitrate was given intravenously, while in Donnelly and Holman's work the route was subcutaneous. Although comparative studies were not performed, it appears likely that the intravenous administration of uranyl nitrate would be more toxic than the subcutaneous. Karsner, Reimann and Brooks [14] pointed out that when uranium salts are injected subcutaneously a considerable

14. Karsner, H. T.; Reimann, S. P., and Brooks, S. C.: Studies of Uranium Poisoning: III. The Question of Renal Tissue Affinity for Uranium, J. M. Research **39**:169 (Nov.) 1918.

amount probably forms an insoluble precipitate at the site of injection.

The protection of the kidneys from uranium poisoning by sodium citrate does not depend on correction of acidosis, since the latter follows, rather than precedes, severe renal damage. It is probably explained by the fact that the citrate facilitates excretion of the poison, thereby reducing its injurious effect. Much greater amounts of uranium were recovered from the urine of dogs given citrate orally than from the urine of control animals, especially during the first twenty-four hours after the injection of uranyl nitrate. Moreover, histochemical studies, although qualitative, showed retention of uranium in the renal tubules of the control dogs and little, if any, retention by the citrate-treated animals. The action of sodium citrate in promoting excretion of uranium is nonspecific, since sodium bicarbonate and sodium carbonate presumably have the same effect.

A factor possibly related to increased excretion of uranium concerns the $p_H$ at which uranium salts cause precipitation of serum proteins. Although the latter are obviously not identical with renal proteins, they have been used to illustrate in vitro precipitation by uranium salts. The approximate range of precipitation lies between $p_H$ 4 and 7. Under experimental conditions, dog urine has a $p_H$ range of about 4.8 to 8.5 but is usually more acid than $p_H$ 7. Such acidity may permit precipitation and necrosis of renal cell proteins. In contrast, the alkaline $p_H$ in animals treated with sodium citrate may prevent the precipitation of renal protein.

## SUMMARY AND CONCLUSIONS

Dogs receiving sodium citrate, either by the intravenous or by the oral route, can survive an otherwise lethal dose of uranyl nitrate.

When the sodium citrate is given orally in large amount the changes produced in the kidneys by uranyl nitrate are slight and recovery is rapid. In no instance were the renal lesions in such dogs as severe or diffuse as in control animals.

Sodium citrate facilitates the excretion of uranium in the urine, thereby reducing its toxic action. Probably the alkalinizing effect of the citrate does not permit development of the $p_H$ required for precipitation and necrosis of renal protein.

# ANTISPASMODIC ACTIONS OF "HYPOTENSIVE" EXTRACTS ON SMOOTH MUSCLES

ROBERT H. DREISBACH, M.D.; WALTON VAN WINKLE JR., M.D.,* AND P. J. HANZLIK, M.D.

SAN FRANCISCO

Ever since the experimental demonstration by Abelous and Bardier [1] in 1909 that urine contains a "hypotensive" substance, periodically there have appeared favorable clinical reports of therapeutic usefulness of this or that tissue extract in treatment of hypertensive and myospastic states. The clinical usage has been practically limited to insulin-free pancreatic extracts which are also free from histamine and choline, the products most commonly used being depropanex and padutin. These and other similar extracts are not accepted by the Council on Pharmacy and Chemistry of the American Medical Association because of lack of convincing evidence of therapeutic value despite their experimental effectiveness on the circulation.[2] The value of depropanex and padutin in treatment of intermittent claudication [3] and of ureteral colic [4] was formerly, and has been again recently, stressed. The scope of claims for their antispasmodic action has been extended to the relief of pain in angina pectoris and dysmenorrhea [4b] and of symptoms in peripheral arterial disease.[5] A remarkable rapidity in relief of symptoms is sometimes claimed, such as three minutes after injection of depropanex. Unfortunately, the clinical results have not satisfactorily controlled or have been complicated by the conjoint use of an opiate or of some physical maneuver, and therefore the data are not conclusive. However, most clinical reporters do not hesitate to attribute the benefits obtained to an antispasmodic action due to direct relaxation of smooth muscles in the blood vessels, ureter or uterus, as the case may be.

The alleged benefits in clinical circulatory states cannot be reconciled with carefully determined pharmacodynamic actions in intact animals.[6] Administered either orally or intramuscularly, these "hypotensive" extracts in excessive doses are wholly ineffective in animals, but they are effective when administered intravenously.[7] Yet intramuscular injection and oral administration are used clinically, and intravenous injections warned against. However, a fall in blood pressure after intravenous injection of these extracts into animals has been the exclusive criterion of their clinical efficacy. Super-

* At present, Senior Medical Officer, Drug Division, Federal Security Agency, Washington, D. C.

From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine.

1. Abelous, J. E., and Bardier, E.: Urohypotensine, J. de physiol. et de path. gén. **40**:777, 1909.

2. Map and Myoston Not Acceptable for N. N. R., report of the Council on Pharmacy and Chemistry, J. A. M. A. **111**:321, (July 23) 1938.

3. (*a*) Fatherree, T. J., and Hurst, C.: Intermittent Claudication: Its Treatment with an Insulin-Free, Deproteinated Pancreatic Extract (Depropanex), Ann. Int. Med. **17**:325, 1942. (*b*) Klein, C.; Saland, G., and Zurrow, H.: Pancreatic Tissue Extract (Insulin-Free) in the Treatment of Peripheral Disease, ibid. **18**:214, 1943. (*c*) Fisher, M. M.; Duryee, A. W., and Wright, I. S.: Deproteinated Pancreatic Extract (Depropanex): I. Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, Am. Heart J. **18**:425, 1939. (*d*) Barker, N. W.; Brown, J., and Roth, I.: Effect of Tissue Extracts on Muscle Pains of Ischemic Origin (Intermittent Claudication), Am. J. M. Sc. **189**:36, 1935. (*e*) Roth, G. M.; Barker, N. M., and Brown, G. E.: Effect of Pancreatic Tissue Extract on Muscle Pain of Ischemic Origin (Intermittent Claudication), Proc. Staff Meet., Mayo Clin. **8**: 481, 1933.

4. (*a*) Walther, H. W. E., and Willoughby, R. M.: The Use of Deproteinated Pancreatic Extract in the Treatment of Ureterospasm, New Orleans M. & S. J. **95**:182, 1942. (*b*) Duncan, I. G.: Our Experience with Depropanex, Memphis M. J. **16**:182 (Dec.) 1941. (*c*) Carroll, G., and Zingald, F. G.: A Clinical Experimental Study of the Effect of Pancreatic Tissue Extract on the Ureters, South. M. J. **31**:233, 1938. (*d*) Neptune, H. E.: Use of Deproteinated Pancreatic Tissue Extract (Depropanex) in Ureteral Catheterization, J. Kansas M. Soc. **42**:474, 1941.

5. Gorhan, L. W., and Climenko, D. R.: Role of Insulin-Free, Histamine-Free Pancreatic Tissue Extract in Treatment of Peripheral Arterial Disease, Am. Heart J. **25**:486, 1943.

6. Lehman, A. J., and Van Winkle, W., Jr.: Depressor Effects from Urine and Tissue Extracts: Comparisons of Different Species, Vasomotor Changes and Related Chemical Agents, Arch. internat. de pharmacodyn. et de thérap. **59**:75, 1938. Van Winkle, W., Jr., and Lehman, A. J.: Pressor Effects from Urine and Tissue Extracts Including Comparisons of Vasomotor Changes and Related Chemical Agents, ibid. **59**:133, 1938.

7. Van Winkle, W., Jr.: and Intramuscular Ineffectiveness of "Hypotensive" Extracts, Proc. Soc. Exper. Biol. & Med. **46**:220, 1941.

ficially, this might appear to possess a predictable therapeutic value in vasospastic states, but actually a depressor action of these extracts is not paralleled by a generalized vasodilation, including dilation of peripheral vessels of extremities and vessels of viscera. Treatment directed at vasospasm is generally regarded as unsatisfactory in conditions such as intermittent claudication; hence, even if an extract caused peripheral vasodilation it would not necessarily be beneficial. The results reported by Barker, Brown and Roth,[3d,e] by Fatherree and Hurst [3a] and by Klein Saland and Zurrow [3b] are practically in agreement with this, although improvement in this clinical condition is, nevertheless, attributed by these reporters to the extracts used. Since these extracts are widely exploited for use in treatment of severe conditions and benefits alleged which are ascribed to an antispasmodic action directly on smooth muscles, it appeared worth while to test the validity of this claim. This was done with the two extracts most commonly used, depropanex and padutin, on the smooth muscles of various isolated organs. A summary of the results obtained is presented in this report. Briefly, this shows that the smooth muscles tested are not demonstrably affected by low concentrations (well above possible therapeutic levels, however) but are stimulated, if anything, by high concentrations such as could not possibly be attained in the body with the doses recommended.

## METHODS

Records were made on a slow kymograph of the motor activity of different organs suspended in a bath of oxygenated Locke-Ringer solution kept at 38 C. For comparison, the tissue extracts or their preservatives in saline solution, were added directly to the bath. The solution in the bath was usually changed between applications. The extracts used were depropanex, which is claimed to be deproteinated pancreatic extract, and padutin, which is obtained from pancreas or urine. The preservative in depropanex is 0.25 per cent phenol, while that in padutin is about 50 per cent glycerin. Both extracts caused typical depressor effects when injected intravenously into rabbits, which was positive proof of their pharmacologic potency.

The following tissues obtained from dogs and rabbits were used: circular muscles of the abdominal aorta, common carotid and femoral arteries, longitudinal muscle of the small intestine, circular muscle of the ureter and strips of bladder fundus. Epinephrine was applied to blood vessels and acetylcholine to the other organs to determine their functional activity, and the results with those not reacting typically were rejected. The tissue extracts were also tried on spastic contractions of ureteral muscle produced by barium chloride or acetylcholine. In order to determine whether the action of these tissue extracts was directly on the muscle or on the intrinsic nerves, atropine was used to paralyze the parasympathetic nerves of the intestine and bladder, ergotamine to paralyze the augmentor sympathetic nerves of arteries and nicotine to block intrinsic ganglions of the intestine. A total of 230 tests was made on fifty-five isolated organs. A comparable number of tests with the preservatives alone was made on the same organs. The essential results obtained may be summarized according to the two products tested, as there were some differences in the reactions.

## RESULTS

*Padutin.*—This product as well as its preservative, 50 per cent glycerin, almost invariably depressed smooth muscle of the intestine, ureter and blood vessels. The concentration of the product or of glycerin necessary to produce a decrease in intestinal activity was from 1:80 to 1:320. Below a concentration of 1:160, the product or glycerin was ineffective on blood vessels and ureter. From this it follows that the depression of smooth muscles in these organs was predominantly due to the preservative.

*Depropanex.*—This extract and its preservative, 0.25 per cent phenol, increased the tonus and amplitude of contractions of small intestine. This effect was not abolished by atropine or nicotine. Hence the stimulant effect appeared to be directly on the smooth muscles of this organ and was due to the phenol. The extract increased the tonus of both bladder and arterial muscles. Similar concentrations of 0.25 per cent phenol depressed or had no demonstrable effect on bladder muscles, but arterial muscles were unaffected by the preservative. The stimulation of arterial muscles was not abolished by administration of ergotamine, while that due to epinephrine disappeared, as usual. The bladder muscles continued to be stimulated by depropanex after atropine was given. Thus, the stimulation of bladder and arterial muscles with depropanex was due to direct action of the drug on the smooth muscles independently of the preservative. The minimal effective concentrations of depropanex were 1:1,600 on blood vessels and 1:400 on the bladder. Epinephrine and acetylcholine in concentrations of 1:40,000,000 usually produced their typical effects on the blood vessels and on the bladder, respectively, which showed that the smooth muscles of these organs functioned satisfactorily. Depropanex and 0.25 per cent phenol in concentrations of 1:80 showed the spontaneous contractions as well as decreased the activity produced by the applications of barium or acetylcholine in isolated ureters, and therefore the depression was due to the preservative. The extract was ineffective below a concentration of 1:80. Obviously depropanex affects various smooth muscles somewhat differently, the arterial

and bladder muscles being stimulated independently of the preservative while intestinal and ureteral muscles, whether normal or excited, are unaffected except for actions of the preservative.

## COMMENT

Clearly the results of these direct tests with padutin and depropanex on the different isolated organs used do not sustain the clinical claims that the therapeutic benefits are due to an antispasmodic action as a result of depression or inhibition of smooth muscles. On the contrary, arterial and bladder mucles were stimulated, if anything, by depropanex. However, the concentrations necessary for this were about twenty to sixty times the theoretic concentration after single doses of 2 to 3 cc. intramuscularly in a 70 Kg. adult, complete absorption and even distribution in the body being assumed, which probably could not be attained. Actually, the concentrations reaching smooth muscles *in situ* would probably be much less, and these were found ineffective on these isolated muscles. According to the same assumptions, intestinal and ureteral muscles were unaffected by tissue concentrations up to four hundred times the theoretic after the clinical doses used. Higher concentrations caused no more depression than the preservative. Padutin was found to be devoid of intrinsic effects on intestinal, ureteral and vascular muscles, except for the depression caused by the preservative, glycerin, but this occurred with concentrations of over four hundred times the theoretic on the basis of 1 cc. intramuscularly in a 70 Kg. adult. Our results on intestinal muscle do not agree with the claim of Werle, Gotze and Keppler [8] that this product, under name of "callicrein", stimulates isolated dog intestine.

It follows from all this that depropanex and padutin in concentrations of the order of the clinical dose recommended for intramuscular injection are devoid of intrinsic therapeutic merit in colicky states of smooth muscles, such as those of the ureter, the intestine and presumably the uterus and in vasospasm and related disorders, such as intermittent claudication and other vascular disease. Our demonstration of the ineffectiveness of these agents is in agreement with Van Winkle's [7] demonstration of their ineffectiveness on the circulation and of a lack of toxicity after excessive doses given intramuscularly and orally. Curiously, the use of these agents by the only method of administration which produces definite and sometimes profound circulatory and visceral effects, namely, the intravenous, is warned against. With this method the effects are the result chiefly of splanchnic vasodilatation with a pooling of blood in the abdominal viscera, in which the fundamental action is a direct inhibition or depression of vascular smooth muscle, intestinal vessels being especially reactive. The depressor action may be profound and well sustained, and presumably for that reason intravenous injection is regarded as too hazardous for clinical use.

As for some other possible basis for the claimed clinical benefits when these extracts are injected intramuscularly, the local irritation of the preservatives which they contain should not be overlooked. Most clinical reporters state that the injections cause stinging or irritation locally in patients. Local irritation might be expected from 0.25 per cent phenol, which is present in depropanex, and from 50 per cent glycerin, present in padutin. Since the recommended dosage of these extracts would not be expected to result in systemic effects of phenol or glycerin, it would be the local irritation which could conceivably cause diversion of attention or some reflex inhibition, which might be responsible for subjective relief in a patient with pain. The unusually rapid relief, in three minutes, after injection claimed by some clinicians would fit in with some reflex or subjective action rather than with direct and objective effects. This could not be tested satisfactorily in animals, but it is suggested as a possibility for human subjects, who are more sensitive. However, this still leaves the status of these hypotensive extracts unchanged as being agents without demonstrable intrinsic therapeutic merits, according to the dosage and methods of administration used.

## CONCLUSIONS

Results of extensive tests on different isolated organs with two "hypotensive" extracts, depropanex and padutin, which are claimed to relieve symptoms from vasospasm and other vascular disease, such as intermittent claudication and angina pectoris, and pain of ureteral colic and dysmenorrhea, failed to sustain clinical claims that these agents produce an antispasmodic action as a result of direct inhibition or depression of smooth muscles.

Concentrations of padutin over 400 times the possible theoretic tissue levels based on clinical dosage were necessary to produce some depression of intestinal, ureteral and vascular muscles,

8. Werle, E.; Gotze, W., and Keppler, A.: Effect of Callicrein on the Isolated Intestine and a New Substance Stimulating the Intestine, Biochem. Ztschr. **289**:217, 1937.

but the same effect was produced by the preservative, glycerin, in this product. The same was true for depropanex and its preservative, phenol, for intestinal and ureteral muscles.

Depropanex independent of the preservative caused stimulation, if anything, of arterial and bladder muscles with concentrations twenty to sixty times the theoretic concentration based on the recommended clinical dosage. Lower concentrations were devoid of demonstrable effects, which also was true for padutin.

The ineffectiveness of these agents on smooth muscles is in accord with their ineffectiveness intramuscularly and orally on the circulation and with their lack of toxicity in animals, which, however, react definitely to intravenous injection, a method warned against clinically.

Local irritation from the preservatives when these extracts are injected intramuscularly has a possible contributory effect in promoting relief from clinical symptoms.

However, an objective experimental basis for the use of depropanex and padutin is lacking, and these extracts are believed to be devoid of intrinsic therapeutic merits with the dosage and methods of administration used.

# DIFFERENTIAL ROLES OF LAYERS OF HUMAN EPIGASTRIC SKIN ON DIFFUSION RATE OF WATER

TRAVIS WINSOR, M.D., AND GEORGE E. BURCH, M.D.
NEW ORLEANS

It has long been recognized that the skin is responsible for preventing excessive loss of water from the body. In severe burns the fluids of the body are readily lost, and serious alterations in the electrolyte balance within the body result. Although the water-withholding function of the skin has long been generally recognized, there has not been, to our knowledge, any detailed study which attempted to determine which layer or layers of the skin are responsible for retarding loss of water through this structure. The following experiments were carried out to determine which layer of the skin is chiefly responsible for retention of water.

The terms diffusion water and sweat are used in these discussions as defined in a previous publication.[1] The term diffusion water indicates water that has passed through the skin to the atmosphere by the process of diffusion; it does not include water secreted onto the surface of the skin by the underlying sweat glands. The term sweat indicates water secreted onto the surface of the skin by the activity of the sweat glands, no matter how slow the rate of secretion.

In performing the following experiments we found it convenient to consider the tissues studied as consisting of three distinct units. These are: (1) the epidermis, (2) the dermis and (3) the underlying tissues, which consist of fascia, muscle and peritoneum.

## MATERIALS AND METHODS

The method used for collecting the water of diffusion has been described elsewhere[2] and may be summarized as follows: A small brass chamber fitted with an inlet and an outlet tube was sealed over the surface for study so as to isolate a known area (5 sq. cm.). Dry oxygen was passed through the inlet tube into the collecting chamber, where the water vapor was collected. The oxygen laden with water vapor was returned through the outlet tube and passed through aluminum coils, where the vapor was caught and retained by freezing. The coils were weighed before and after collection of the water.

In studying the rate of diffusion of water through dead skin a specially constructed box was used, as previously described.[1] The box, which had a water jacket, contained isotonic solution of sodium chloride, into which the skin to be studied was submerged. The temperature of the skin and of the solution was varied by raising or lowering the temperature of the water jacket. The temperature of the skin was measured by means of a thermometer placed in the saline solution.

The rate of diffusion of water through certain layers of the epidermis was studied by producing a blister on the epigastrium of the subject by means of a cantharides plaster and collecting the fluid from the surface of the top of the blister. The method of using cantharides as a vesicant for experimental purposes has been reviewed and summarized by Benedek.[3] The procedure employed by us was as follows: A sufficient amount of cantharides cerate was applied to a small piece of cotton cloth to cover an area of approximately 5 or 10 sq. cm. This plaster was then taped to the subject's epigastrium for approximately ten hours, when the plaster was removed. A well formed blister was usually present at this time. Twelve hours after the plaster had been removed, during which time the mild inflammatory reaction subsided, a collecting chamber was sealed to the top of the blister and the collection of the water of diffusion was carried out.

All studies on living subjects and dead skin were conducted in an air-conditioned room. The temperature and the relative humidity of the room were maintained at 75 ± 1 C. and 50 ± 2 per cent respectively. Each patient was clothed in a cotton gown and was covered with a light sheet, so that he was slightly cool but comfortable. The brass collecting chamber isolating a known area of skin for study was sealed to the skin of the epigastrium, and ten minute collections were made as described.

Thirteen adult patients, 7 white and 6 Negro, were chosen for study. Ten were females, and 3 were males. All patients had had complete physical examina-

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This is the seventh paper published from this Laboratory of Tropical Physiology.

From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans.

1. Burch, G. E., and Winsor, T.: Rate of Insensible Perspiration (Diffusion of Water) Locally Through Living and Through Dead Human Skin, Arch. Int. Med., this issue, page 437.

2. (*a*) Burch and Winsor.[1] (*b*) Burch, G. E., and Sodeman, W. A.: Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, Am. J. Physiol. **138**:603, 1943. (*c*) Neumann, C.; Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas, with Results for the Finger Tip, Toe Tip and Postero-Superior Portion of the Pinna of Normal Resting Adults, Am. J. Physiol. **132**:748, 1941.

3. Benedek, T.: The Cantharides Blister and Its Application in Microbiological Research: A Review of the Literature and Some Suggestions, J. Trop. Med. & Hyg. **42**:81, 1939.

tions and were without cutaneous diseases. The segments of epigastric skin of 11 cadavers were removed from the bodies as soon after death as possible. Six of the skins were from white and 5 from Negro bodies.

## EXPERIMENTS

EXPERIMENT 1: *The Rate of Diffusion Through the Full Thickness of the Abdominal Wall of the Epigastrium of Living and of Dead Human Subjects.*

A. The following studies were carried out on 7 white and 6 Negro patients. Each was placed in bed in the comfortable air-conditioned room. The collecting chamber was sealed to the abdominal skin above the umbilicus, and collections of the water of diffusion were made after the patients had rested for at least sixty minutes. Repeated collections at intervals of ten minutes each were made as in previous studies.[2a, b]

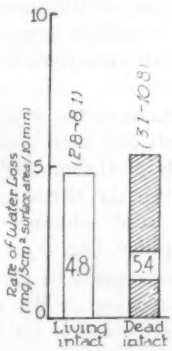


Fig. 1.—The rate of diffusion through the layers of the epigastrium of 13 living subjects and through the isolated abdominal wall, epidermis, dermis and underlying tissues of 10 cadavers. In this figure and all to follow, the mean values are indicated in the center of each column and the extremes at the top.

The average rate of diffusion for the 13 subjects resting quietly in a comfortable room was 4.8 mg. per 5 sq. cm. of surface area per ten minutes, and the maximum and minimum rates were 8.1 and 2.8 mg. respectively (fig. 1). The mean rate of diffusion through the abdominal wall of the white subjects was 6.7 mg. per 5 sq. cm. per ten minutes, and the extremes were 2.8 and 8.1 mg. respectively. The mean rate in the Negro group was 4.4 mg., and the extremes were 6.7 and 3.0 mg. (fig. 2).

B. Segments of the complete thickness of the abdominal wall of 6 white and 4 Negro cadavers were removed as soon after death as possible. These skins were either studied immediately or allowed to stand in the refrigerator before using for a period varying from a few hours to thirty days. The effect of storage of skin on the diffusibility of water through it and the methods used for studying the rate of diffusion through the dead skin have been reported elsewhere.[1] A collecting chamber was sealed on the surface of the skin, and after drying of the cement both were placed in the saline bath, which was kept at approximately 33 C.

The results are shown in figures 1 and 2. The average rate of diffusion for all 10 dead abdominal walls was 5.4 mg. per 5 sq. cm. of surface area per ten minutes, and the extremes were 3.1 and 10.8 mg. There was no significant difference between the diffusibility of the water through the living and through the dead abdominal walls. The rate of diffusion through the entire abdominal wall of the living Negro appeared slightly less than the corresponding value for the white group, but this slight difference may be explained by the small number of subjects studied.

It is well to point out that in the living subjects the water that diffused through the skin to the exterior most likely had its origin from the blood of the skin and did not diffuse through the entire thickness of the anterior abdominal wall. It is quite likely that in the dead abdominal wall some water diffused through its entire thickness from the bath of saline solution.

That this fluid represents the water of diffusion and not the water of sweat has been demonstrated at length elsewhere.[1] A few of the important points which establish this fact may be summarized as follows: 1. The rate of loss of water through living skin in a comfortable, cool environment is not significantly different from that through dead skin at body temperature. 2. The rate of flow of fluid through dead skin can be increased slightly by increasing the cutaneous temperature from 11°C. to 45.5 C. In the living patient there is little increase in rate of diffusion of fluid until the

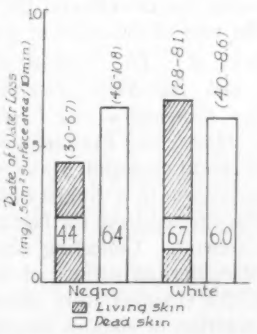


Fig. 2.—The rate of diffusion through the layers of the epigastrium of Negro and white living subjects and through the isolated abdominal wall (epidermis, dermis and underlying tissue) of Negro and white cadavers.

room temperature is elevated to a certain point, when a sudden marked increase in rate of flow is encountered because of the activity of the sweat glands. 3. The rate of diffusion of water through the top of a blister in which the glomerular portion of the sweat glands is absent is not significantly different from the rate of diffusion through living intact skin. 4. The rate of diffusion of water through the skin of patients

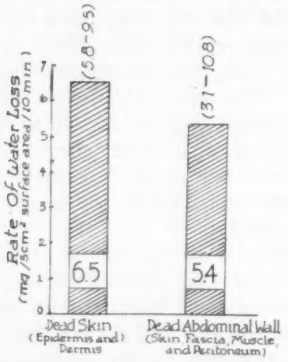


Fig. 3.—The rate of diffusion through the epidermis and dermis after removal of the tissues ordinarily underlying the dermis (fascia, muscle and peritoneum).

with atrophic sweat glands is of the same level as that through the skins of normal persons in a comfortable environment.

The next experiment was carried out to determine what effect the tissues underlying the skin—the fascia, the muscle and the peritoneum —have on the rate of diffusion of water.

EXPERIMENT 2: *The Rate of Diffusion of Water Through the Skin (Dermis and Epidermis) After Removal of the Underlying Tissues (Fascia, Muscle and Peritoneum).*—A patch of skin, dermis and epidermis was dissected from the epigastric region of a Negro cadaver so that the skin was separated from the fascia, the muscle and the peritoneum. Collecting chambers were sealed to the epidermal surface of the skin, and the skin and the chamber were placed in a bath of isotonic solution of sodium chloride at 33 C. Repeated ten minute collections were made.

The results are shown in figure 3. The mean rate of diffusion through the isolated skin was 6.5 mg. per 5 sq. cm. per ten minutes, and the extremes were 5.8 and 9.5 mg.

It is apparent that there was no significant difference between the rate of diffusion through the whole thickness of the abdominal wall and that through the skin which had been dissected free from the underlying tissue.

The next experiment consisted of a study of the rate of diffusion through the dermis (the corium) with the epidermis first partly and then completely removed.

EXPERIMENT 3: *The Rate of Diffusion of Water Through (1) the Dermis (Corium) of Dead Skin and (2) the Dermis and the Deeper Layers of the Epidermis Combined in Living Skin.*

A. The epidermis of isolated dead skin was removed by scraping with a scalpel the skin of 2 cadavers. The collecting chambers were sealed over these areas, and the skins and chambers were placed in a bath of isotonic solution of sodium chloride maintained at a constant temperature of 30 C.

The average rate of diffusion was 32.4 mg. per 5 sq. cm. of surface area per ten minute period, and the extremes were 21.1 and 43.7 mg. (fig. 4).

Histologic sections of the scraped area showed that the epidermis had been removed. In some areas a few cells of the malpighian layer were seen lying between the dermal papillae, and in some areas the basal columnar layer was seen covering the papillae (fig. 5).

This experiment tends to show that the diffusion-restraining layer of the skin is confined to those structures which lie within the epidermis.

B. In each of 6 patients a blister was raised on the epigastric skin with a cantharides plaster. The plaster was removed, and the top of the blister was removed by cutting around the edge of the blister with a pair of small skin scissors. The raw surface was dried by gently applying

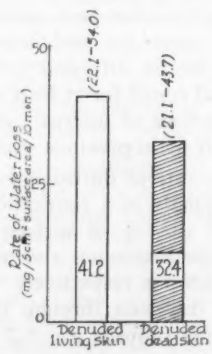


Fig. 4.—The rate of diffusion through the dermis and the tissue underlying the dermis after the epidermis had been removel by scraping the surface of the dead skin and after removal of the top of a blister raised by means of a cantharides plaster.

gauze to the denuded surface, and ten minute collections were made.

The average rate of diffusion through the denuded surface measured approximately thirty minutes after the top of the blister had been removed was 41.2 mg. per 5 sq. cm. per ten minutes, and the extremes were 54.0 and 22.1

(fig. 6). In general, the rate of loss of water decreased daily and finally reached the basal level.

According to Benedek,[3] the epidermis remaining in the denuded surface after removal of the top of a blister produced by a cantharides plaster consists histologically of the stratum germinativum, the malpighian layer and a few cells of the stratum spinosum.

This experiment shows that that part of the epidermis superficial to the stratum spinosum contains the layer mainly responsible for the inhibition of rapid diffusion of water.

C. At this time it seemed of interest to determine the rate of diffusion through various isolated tissues of the body which possess no epidermal layer. The collecting chambers were sealed to the epicardial surfaces of the left ventricle, to the splenic capsule of the spleen, to the visceral pleura of the left lung and to the interior of a segment of the thoracic aorta. These organs were placed in the saline bath at a constant temperature of 33 C., and collections of water were made.

The results are shown in figure 7. The rate of loss of water through the heart, the spleen, the lungs and the aorta was 19.4, 34.0, 37.4, and 43.7 mg. per 5 sq. cm. per ten minutes respectively.

In general the fluid passed through these organs as readily as it passed through dead and living skin devoid of the epidermis. In no instance did any of these organs inhibit the diffusion of fluid to the same degree as did the living or the dead skin with the epidermis intact (fig. 6). These results indicate that the epidermis is of paramount importance as an organ resisting the diffusion of water.

EXPERIMENT 4: *The Rate of Diffusion of Water Through the Superficial Layers of the Epidermis.*

A. Blisters were raised on the abdominal skin of 4 Negro and 2 white patients with the cantharides plaster as already described. The blisters raised were made somewhat larger than 5 sq. cm. in area, so that the collecting chambers could be sealed to the top of the blister itself.

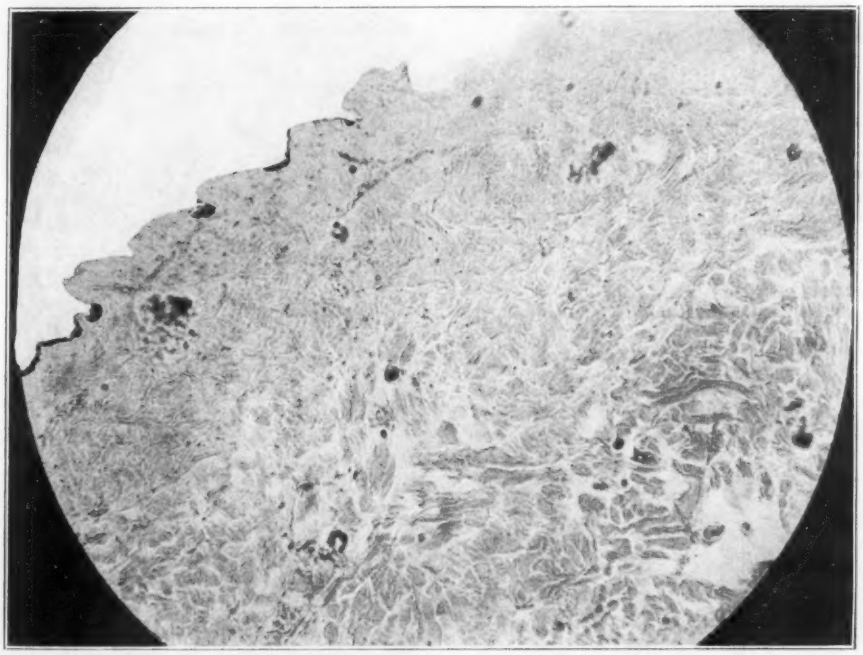

Fig. 5—The tissue shows the dermis after removal of the epidermis by scraping. The epidermis has been almost completely removed except for a few isolated cells of the stratum germinativum located between the dermal papillae.

After the inflammatory reaction had subsided the diffusion water was determined at intervals of ten minutes.

The results are shown in figure 8. The average rate of diffusion was 4.5 mg. per 5 sq. cm. per ten minutes, and the maximum and minimum rates were 6.0 and 3.0. The rate of diffusion through normal intact living skin was 4.8, the extremes being 2.8 and 8.1.

Histologically [4] the top of the blister consisted of keratinized epithelial cells which overlay an

4. Dr. Granville A. Bennett and Dr. Charles E. Dunlap interpreted the histologic sections.

irregular layer of necrotic and seminecrotic epithelium. The epithelial cells were separated by edema fluid and fibrin. This layer varied from 1 to 8 cells in thickness. Adherent to the under surface of this cellular layer was a mass of fibrin and edema fluid containing unidentifiable cells, the contents of the blister (fig. 9).

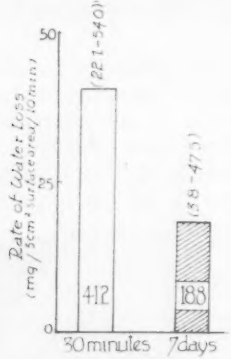


Fig. 6.—The rate of diffusion through the dermis, the tissue underlying the dermis and a few cells of the malpighian layer which formed the floor of the blister cavity thirty minutes and seven days respectively after removal of the top of the blister.

There was no significant difference between the rate of diffusion through the top of the blister and through the adjacent intact skin of subjects resting quietly in a comfortable environment.

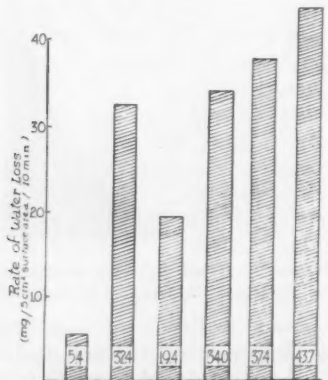


Fig. 7.—The rate of diffusion through various organs of the body which possess no cornified epithelium similar to that of the skin.

This experiment shows that the epidermis superficial to the stratum spinosum contains the diffusion-inhibiting barrier of the skin.

Because of the high content of protein of the blister fluid it was thought that the osmotic pressure within the blister prevented the loss of fluid through the epidermis which had been raised by the vesicant. In order to clarify this point the next study was made.

B. By carefully excising the top of the blister used in the foregoing experiment around the edge of the collecting chamber sealed to it, it was possible to transfer the collecting chamber with the top of the blister intact and attached into the saline bath at 33 C. (fig. 10). Several ten minute collections were made.

The mean rate of diffusion was 4.2 mg. per 5 sq. cm. of surface area per ten minutes, and the extremes were 3.8 and 4.7 mg. (fig. 8).

The rate of diffusion of the blister fluid through the top of the blister and the rate of diffusion of water from the saline bath through the top of the blister were not significantly different; this fact ruled out the possibility of any inhibiting influence from the colloids of the blister fluid.

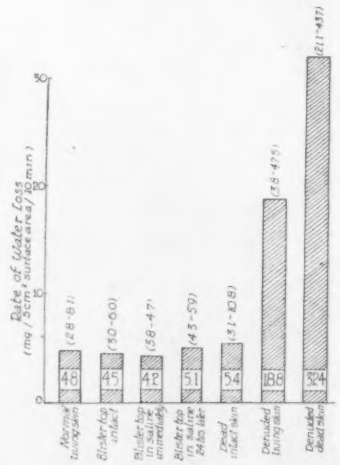


Fig. 8.—The rate of diffusion through the top of a blister raised by means of cantharides cerate.

C. As it was felt that living cells underlying the corneum might be responsible for the retardation of the diffusion water, the top of the blister was allowed to stand in the refrigerator intermittently for four weeks to allow death of the cells adjacent to the corneum to take place. The rate of diffusion was again determined in the saline bath. The rate was not essentially different from that encountered in part B of this experiment (fig. 8).

It is therefore unlikely that underlying cells which are living have any influence on the rate of diffusion of water through the epidermis, for when these cells were dead the rate of diffusion remained unaltered.

D. It was thought that the cantharides might have altered the superficial layer of the top of the blister so that water diffused through it less readily. To study this possibility the superficial

layer of the skin (the corneum) was removed by sandpapering with no. 00 sandpaper. The skin of 1 patient was abraded lightly, the skin of 4 patients was abraded moderately and the skin of 2 others was abraded heavily. In no instance was the abrasion sufficiently intense to produce pain or discomfort. It was felt that the light sandpapering removed little of the corneal layer, that the moderate sandpapering removed part of the corneum and that the heavy sandpapering removed all of the corneum. After the immediate hyperemia had subsided a collecting chamber was sealed over the sandpapered area, and ten minute collections of the diffusion water were made.

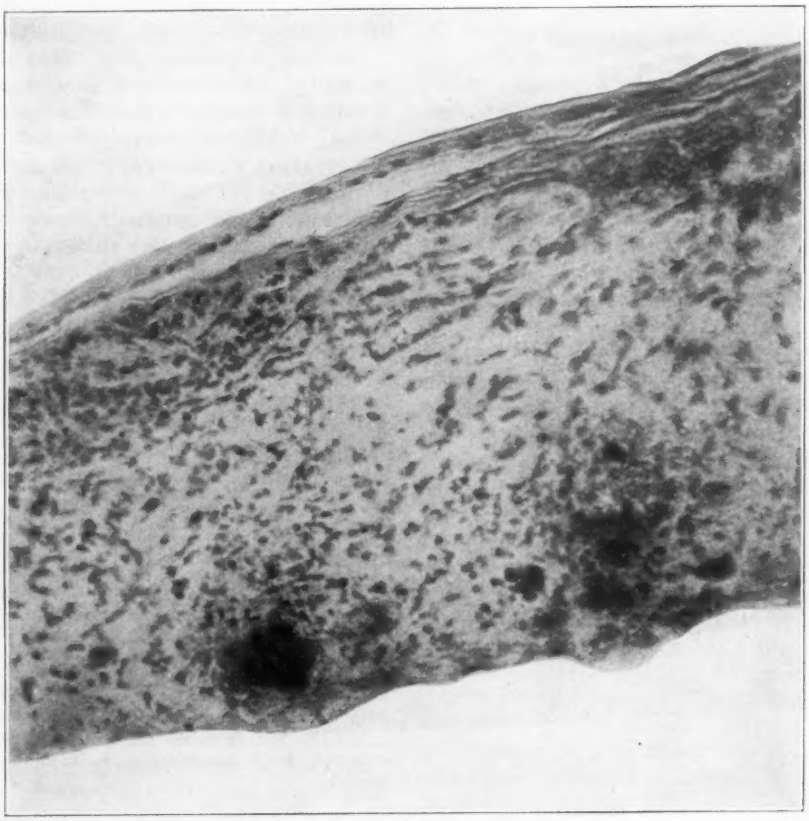

Fig. 9.—The top of the blister, consisting of the stratum corneum and a few inflamed cells underlying this layer.

The results are shown in figure 11. The mean rate of loss of water for light sandpapering was 5.7 mg. per 5 sq. cm. per ten minutes; the mean rate for moderate sandpapering was 16.3 mg., and the mean rate for heavy sandpapering was 48.0 mg. The extreme rates are shown in the figure.

Removal of the corneal layer by sandpapering resulted in a marked increase in the rate of diffusion of water above that in intact skin—a rate comparable to those found for skin deprived of its epidermis or of the superficial layer of the epidermis. It would appear, therefore, that the corneum is the layer of the skin mainly responsible for the inhibition of diffusion. It is necessary, however, that two other possible factors be eliminated before any such conclusion can be drawn. They are: (1) the influence on diffusion of the hyperemia produced by sandpapering and (2) the influence on diffusion of the lipid materials on the surface of the skin. These two factors are discussed in the 2 experiments immediately following.

E. The abdominal skin of 2 patients was rubbed vigorously with a piece of gauze. The skin was rubbed sufficiently hard to produce definite erythema. There was no evidence that a significant amount of the corneum was removed. A collecting chamber was sealed over the irritated area, and 5 ten minute collections were made.

The rate of loss of water through this abraded area was 5.6 Gm. per 5 sq. cm. of surface per

ten minutes. The maximum was 5.8 mg., and the minimum was 5.4 mg. (fig. 11).

The rate of loss of water through the abraded area was only 0.8 mg. greater than the loss through normal intact living skin. Therefore, erythema does not in itself markedly increase the rate of diffusion. From these experiments it was felt that the barrier to diffusion lies either within the corneal layer or close to it. As the

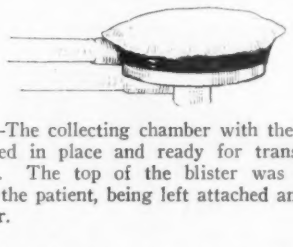

Fig. 10.—The collecting chamber with the top of the blister sealed in place and ready for transfer to the saline bath. The top of the blister was gently cut away from the patient, being left attached and sealed to the chamber.

fats and oils of the skin exist in close proximity to the corneum, the following study on the effect of these substances on the rate of diffusion was executed.

EXPERIMENT 5: *The Rate of Diffusion Through Living Skin After Removal of the Superficial Lipids of the Skin with Acetone and Ether.*—The abdominal skin of 6 patients was treated by rubbing the skin lightly with gauze saturated with acetone and then with ether. This procedure was repeated four or five times in an effort to remove the fats and oils of the

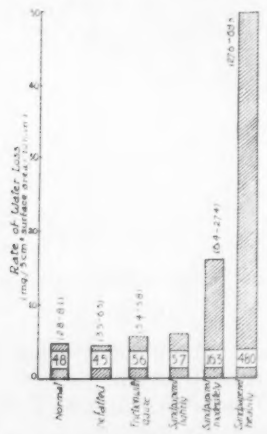


Fig. 11.—The rate of diffusion after removal of various amounts of the corneum by sandpapering, after production of an erythema without removal of the corneum and after washing of the lipid materials from the surface of the skin.

skin. The collection chamber was sealed over the defatted area, and ten minute collections were made.

The average rate of diffusion through the defatted area was 4.5 mg. per 5 sq. cm. of surface per ten minutes, and the extreme rates were 6.5 and 3.5 mg. (fig. 11).

As there was a difference of only 0.3 mg. per 5 sq. cm. per ten minutes between the rate of diffusion through the defatted skin and that through the normal skin, it was felt that the fatty substances in the skin are not responsible for any significant amount of retention.

The 5 experiments described, therefore, have pointed to the corneum as the structure chiefly responsible for the inhibition of loss of water by diffusion.

The next experiment was added to compare the rate of diffusion through the various layers of skin in man with the rate of diffusion through "skins" of various plants, fruits and vegetables.

EXPERIMENT 6: *The Rate of Diffusion Through the "Skins" of Various Fruits and Vegetables.*—The external surfaces of 9 leaves, fruits and vegetables were studied by sealing the collecting chambers on their external surfaces. The following plants were studied: squash, Irish

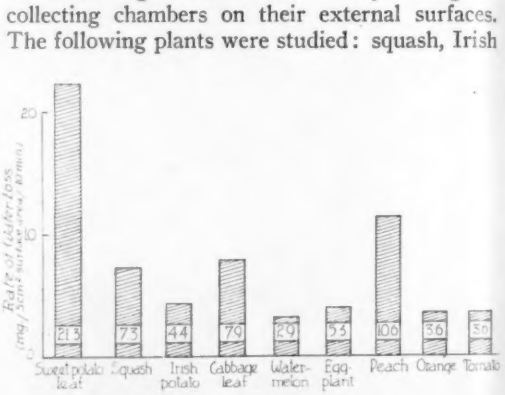


Fig. 12.—The rate of diffusion through the skins of various leaves, fruits and vegetables, which probably have some type of diffusion-inhibiting membrane. The loss from leaf is much the greatest. This is to be expected, since transpiration is rapid through most leaves.

potato, superior surface of isolated cabbage leaf, superior surface of intact sweet potato leaf, egg-plant, watermelon, peach, orange and tomato. The results are shown in figure 12.

It is apparent that the rate of diffusion through these fruits and vegetables was varied. In the watermelon water diffused through its waxy coating at a slower rate and in the peach water diffused at a more rapid rate than it does through living intact human skin.

## COMMENT

The foregoing experiments yielded some interesting information concerning the diffusibility of water through the various layers of the abdominal wall of human subjects. It was found that fluid diffuses with some difficulty through a

section of the whole thickness of the abdominal wall and through the epigastric tissue of a living patient placed in a comfortable, cool environment. From a study of the rate of diffusion through the skin alone, with the underlying tissues removed, it appeared that the cushion of tissue underlying the skin (the fascia, the muscle and the peritoneum) has little effect on the rate of diffusion, as the rate of diffusion through the isolated skin with the underlying tissues removed was not significantly different from the rate through the skin with the underlying tissues attached.

In order to determine the relative effects of the dermis and epidermis on the rate of diffusion, two methods of approach were used. In the first instance isolated epigastric skin of the cadaver was scraped with a scalpel to remove the epidermis; in the second instance certain layers of the epidermis were removed by raising a blister, removing the top of the blister surgically and studying the raw underlying skin thus exposed. In both experiments water diffused rapidly at a rate approximately ten times that through intact skin. It was evident that the diffusion-retarding organ had been scraped from the surface of the dead skin in the one instance and removed with the excision of the top of the blister in the other. Histologic sections of the denuded dead skin showed that the epidermis had been almost completely removed, and sections of the top of the blister revealed the presence of the corneum, with 1 to 8 necrotic cells beneath.

The supposition that the top of the blister contains the diffusion-retarding organ was verified by studying the rate of diffusion through the top of a blister previously raised by means of a cantharides plaster. The rate of diffusion through this membrane was slow and was not significantly different from the rate of diffusion through intact living or dead epigastrium. It was felt, however, that the high protein content of the blister fluid might have offered sufficient resistance to diffusion by virtue of its osmotic pressure to produce an abnormally low diffusion rate. This possibility was investigated by excising the top of the blister and studying the rate of diffusion with the membrane submerged in a saline bath. It was also possible that the cantharides had rendered the top of the blister less permeable than the normal surface of the skin. This possibility was investigated by removal of the corneal layer of the skin with fine sandpaper. The rate of diffusion was rapid in those areas in which the corneum had been removed, and the rate was only slightly accelerated in those areas in which little corneum had been removed. As an area of erythema was produced during the sandpapering procedure, it seemed necessary to study the effect of an artificially produced area of erythema in which the corneum was not removed. This was done by rubbing the skin with gauze without removing any appreciable amount of corneum. An erythema produced in this manner did not increase the rate of diffusion to any noticeable extent. The final experiment was carried out to determine whether it is the corneum itself or the fats and oils on this layer that act as the fluid-retaining barrier. Repeated washing of the skin with alcohol and ether did not raise the rate of diffusion above that in the normal intact living skin. It is felt that of all the layers of the abdominal wall the corneal layer is the one which should properly be called the diffusion-retarding organ of the body surface.

Whitehouse and others [5] have stated that the stratum lucidum is chiefly responsible for the inhibition of diffusion. In these studies it was not possible to demonstrate the stratum lucidum in the sections taken from the epigastrium. This was expected, as it is well known that, while the stratum lucidum is well developed in the palms and the soles, in the skin of the epigastrium it is absent.[6] Therefore, it is the corneum which inhibits diffusion of water. It is possible that the stratum lucidum plays a significant role in the palms and soles.

The keratinized portion of the skin, then, not only serves as a cornified structure which protects the body from physical and chemical injury and infection by virtue of its toughness, but also conserves a considerable amount of water and electrolytes and aids in the maintenance of balance between water and electrolytes. It was noted in a previous study [1] that the length of time since the death of skin (up to a period as long as four weeks) with autolysis of the indulging cells did not influence this inhibition of diffusion of water. This is more or less to be expected, since the corneal layer is made up of dead keratinized cells which will function as a protecting membrane of the body even when the skin is devoid of its circulation and the living cells have died. Although it is dead, it still serves many significant ends in the maintenance of normal functional as well as anatomic states of the body.

The importance of the corneum in the conservation of water and electrolytes in the body is

5. Whitehouse, A. G. R., and Ramage, H.: The Permeability of Human Skin in Electrolytes, Proc. Roy. Soc., London, s.B **113**:42, 1943.

6. Bailey, F. R.: Text-Book of Histology, revised by A. Elwyn and O. S. Strong, ed. 8, Baltimore, William Wood & Company, 1932, p. 306.

certainly increased in hot and humid environments. This is particularly true in the subtropical climates of the southern parts of the United States and in the tropical climates of the world. One can imagine the rapidity with which water might be lost from the body on a windy day in a tropical desert were it not for the inhibition of diffusion by the keratinized layer of the skin.

## SUMMARY

The rates of diffusion of water through living and through dead human skin were measured in an attempt to determine the portion of the skin mainly responsible for inhibiting diffusion. It was possible to rule out the tissues underlying the skin, such as muscle, fascia and fat. The dermis (corium) of the skin was likewise ruled out, as well as the deeper layers of the epidermis and the lipid materials on the surface of the epidermis. It was found finally that the corneum is the most important layer of the skin in inhibiting the diffusion of water. The keratinized layer is responsible for maintaining the loss of water from the surface of the body at a minimum. It is well, therefore, not to consider the dead, cornified layer of the skin lightly, for it plays a most significant role in the conservation of water and electrolytes within the body.

G. Morgavi gave technical assistance in these studies.

# RATE OF INSENSIBLE PERSPIRATION (DIFFUSION OF WATER) LOCALLY THROUGH LIVING AND THROUGH DEAD HUMAN SKIN

GEORGE E. BURCH, M.D., AND TRAVIS WINSOR, M.D.
NEW ORLEANS

There are numerous methods for measuring insensible perspiration by determining total insensible loss of weight.[1] Such methods serve many purposes both clinically and experimentally but have certain limitations. A method which measures insensible loss of water through localized areas of skin often fulfils some of the requirements lacking in methods that measure total insensible loss in weight. The method described by Neumann, Cohn and Burch [2] measures sensible and insensible loss of water through isolated portions of the skin. These observers did not differentiate between the part of water lost insensibly through secretions of the sweat glands and that part lost through diffusion. It is the purpose of this paper to make such a differentiation.

## MATERIALS AND METHODS

Loss of water through isolated areas of living skin was measured by the method previously described.[3] This consisted essentially of the following procedure: Oxygen was dried by being run from a cylinder through aluminum coils cooled in solid carbon dioxide and was then conducted into brass chambers enclosing the parts for study. There the oxygen collected water vapor from the skin. The water-laden oxygen was next conducted to aluminum coils cooled in solid carbon dioxide, where the oxygen was desiccated, the water being condensed in the coils. By weighing the aluminum coils before and after the flow of oxygen the amount of water collected in a given period was determined. By the use of several lines of flow of oxygen many separate areas were studied simultaneously.

To measure the loss of water through dead human skin the same procedure was followed. The brass chambers used to isolate known areas of skin were sealed to the dead skin as previously described.[3b]

By means of a specially constructed water bath the dead skin was kept at any desired temperature. The water bath was constructed as follows (fig. 1): A chamber (*b*) 1 foot (30 cm.) by 1 foot by 1 foot was constructed of 26 gage galvanized iron. A small chamber (*a*), 8 inches (20 cm.) by 8 inches by 8 inches, was constructed and made to fit into the larger box. An inlet and an outlet for water were put into the larger chamber (*b*). The larger chamber was insulated with wood and cork (*d*), and a hinged cover was made of the same insulating materials. (*c*) Isotonic solution of sodium chloride about 1½ inches (4 cm.) deep was placed in the small box (*a*), and a thermometer was inserted through a hole in the cover into the saline solution so that the temperature of the solution could be recorded. By varying the temperature of the water circulated through the large chamber the temperature of the saline bath which contained the pieces of dead skin could be varied. The water circulated through the large chamber was pumped from a 12 gallon (45 liter) water bath controlled either automatically by a refrigerator unit or by adding hot water from the hot tap water circulated into the laboratory. The centrifugal pump which circulated the water had a capacity of 400 gallons per hour. The temperature of the circulated water was controlled to less than 1 degree centigrade.

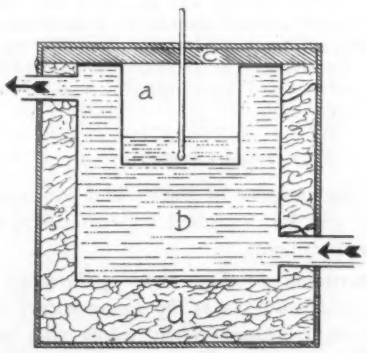


Fig. 1.—A diagram of the cross section of the bath of isotonic solution of sodium chloride used in the study of the dead skins. The bath was kept at a constant temperature. Details are described in the text.

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This is the sixth paper published from this Laboratory of Tropical Physiology.

From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana, New Orleans.

1. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926. Burch, G. E.: A Method for Measuring Small Amounts of Weight Loss in Man, Am. J. M. Sc., to be published.

2. Neumann, C.; Cohn, A. E., and Burch, G. E.: A Quantitative Method for the Measurement of the Rate of Water Loss from Small Areas, with Results for Fingertip, Toetip and Postero-Superior Portion of the Pinna of Normal Resting Adults, Am. J. Physiol. **132**:748, 1941.

3. (*a*) Neumann, Cohn and Burch.[2] (*b*) Burch, G. E., and Sodeman, W. A.: Regional Relationships of Rate of Water Loss in Normal Adults in a Subtropical Climate, Am. J. Physiol. **138**:603, 1943.

The studies were conducted in an air-conditioned room. The temperature and the relative humidity of this room were varied, as is indicated in the individual experiments described in the following section.

These studies were limited to the skin of the epigastrium of living and dead human beings. This area was chosen because it is less likely to show any "nervous" or "psychogenic" sweating than the skin of the hands, axillas, face and neck. The dead skin was collected from 11 subjects (white and Negro), varying in age from a few hours to 80 years, from three hours to seven days after death. A 15 to 20 sq. cm. area of skin was obtained by cutting through the entire thickness of the abdominal wall. The skin was placed in a large Petri dish containing cotton soaked with isotonic solution of sodium chloride. The skin was either covered and transferred to the laboratory for immediate study or stored in a frozen state for future use. The frozen skin was allowed to thaw slowly when being prepared for study.

The living subjects were selected from the wards of Charity Hospital; they were free from any infection or systemic organic condition associated with peripheral vascular disease or cutaneous disease. Two subjects, however, had atrophy of the sweat glands of the skin and complained clinically of being unable to sweat and of suffering considerably from summer weather. Their body temperatures tended to vary with the temperature of the environment.

A cantharides plaster was placed on the skin of the living subjects in order to separate a superficial portion of epidermis from the underlying skin. The method for raising the blisters is described by Benedek.[4] Such blisters were raised, as is indicated in the descriptions of the experiments.

## THE EXPERIMENTS

For the purpose of clarity and continuity, the studies will be described and discussed as separate experiments.

*Experiment 1: The Rate of Loss of Water Through Dead Skin at the Temperature of Normal Living Skin.*—When water was collected from living skin by Neumann and his associates all water which reached the surface of the skin was measured, that is, water which diffused through the skin as well as any water which might be poured onto the surface of the skin through the orifices of the underlying sweat glands. In the present experiment the amount of water that diffused through the skin was measured by determining the amount of water lost through dead skin containing nonfunctioning sweat glands.

Skins from 11 dead subjects were obtained as described, and brass chambers were sealed with rubber cement over the surfaces of the cutaneous areas. After the cement had dried the skins were placed in the saline bath described, with the temperature at 33 C.—approximately the temperature of the skin of the epigastrium of living normal subjects. The rate of loss of water was determined and was found to have a mean of 5.4 mg. per 5 sq. cm. of surface area per ten minutes. The maximum and minimum values were 3.1 and 10.8 mg. respectively.

These values were of the same magnitude as those obtained for the skin of the epigastrium of a living subject in a room at 75 F. (38 C.) with 50 per cent humidity (see experiment 5).

Nine of the 11 specimens of dead skin were from adults and 1 from a 6 year old child; 4 were Negro and 6 white. The mean rate of flow of water through the Negro skins was 6.4 mg. per 5 sq. cm. per ten minutes and through the white

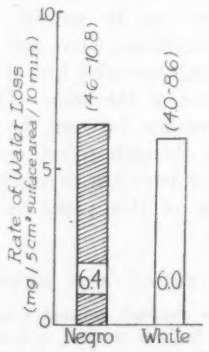


Fig. 2.—The rate of loss of water through dead skin of Negro and white subjects. In this figure and in all figures to follow the mean values are indicated in the center of each column and the extreme values at the top.

skins 6.0 mg. The maximum and minimum values for the Negro skin were 10.8 and 4.6 and for the white 8.6 and 4.0 respectively. There appears to be no significant difference in this respect between the Negro and the white dead skins. The relative values are shown graphically in figure 2.

*Experiment 2: The Influence of Time Between Death of Patient and Freezing and Thawing on Rate of Loss of Water Through Dead Skin.*—Seven of the 11 specimens of skin were studied as in the experiment just described except that measurements of loss of water were made at intervals varying from a few hours to twenty-seven days after the death of the subject. Between successive measurements the skins were stored in the frozen state and then thawed slowly before the next measurement. The first measurements were made from two hours to seven days after the death of the patients.

4. Benedek, T.: The Cantharides Blister and Its Application in Microbiological Research: A Review of the Literature and Some Suggestions, J. Trop. Med. & Hyg. **42**:81, 1939.

The results are shown in figures 3 and 4. A study of dead skins over a period of three weeks, with the skins preserved in an icebox between observations, showed that the rate of loss of water through the skin was not influenced materially by four weeks of storage in a refrigerator (fig. 4). Whether the skins were studied within

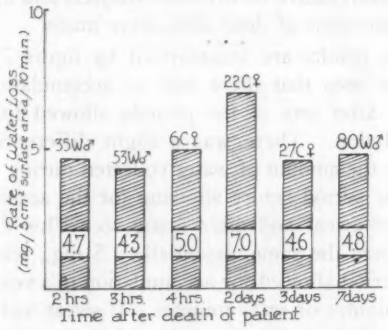


Fig. 3.—The rate of loss of water through 6 specimens of dead skin. The intervals of time between the death of the patient and the taking of the measurement are indicated on the abscissa. The number and letter at the top of each column indicate the age and race of the subject. *W* indicates white; *C*, Negro.

two hours of death or seven days later, the rate of loss of water was virtually the same. Apparently the factors which influence passage of water through the skin are not affected materially by the death of the patient, even over a period of several days, provided the skin is preserved by freezing. Thawing and freezing had no apparent influence.

It is doubtful that any of the water that was collected from the surfaces of the dead skins originated from secretions of the sweat glands. After several days of storage, with intervals of freezing and slow thawing, the cells of the functioning glomerulus of the underlying sweat glands must have been killed. Therefore, the water lost through the skin most probably was water that had diffused through the skin and not water that had been actively secreted by sweat glands.

If we assume that the sweat glands are still living within two to three hours after the subject's death, these experiments show that the sweat glands are not secreting shortly after death (fig. 3).

*Experiment 3: The Influence of the Temperature of the Dead Skin on the Rate of Loss of Water Through the Skin.*—The influence of the temperature of the dead skin was studied for the 11 specimens of skin. The experiments were conducted as in the previous two groups of studies except that the temperature of the bath of isotonic solution of sodium chloride was varied from as low as 11 C. to as high as 45.5 C. In some instances, instead of the skin's being submerged in the saline bath with the cup sealed in place, it was placed in a Petri dish on cotton soaked with isotonic solution of sodium chloride, and the temperature of the entire observation room was increased to levels of from 24 to 45 C., with the relative humidity at 75 to 85 per cent. This was done in order to control the influence of the abnormal amounts of water of the saline bath.

The results are summarized in figure 5. It can be seen from this figure that as the temperature of the skin was increased the rate of loss of water through the skin increased. The temperature effects were essentially the same whether the skin was studied in the saline bath or on a Petri dish in the observation room.

Because of the method used, it was impossible to study the effects of very low temperatures on loss of water through the skin. At low temperatures the water tended to condense in the oxygen lines.

*Experiment 4: A Simultaneous Study of Loss of Water Through Living Intact Skin and Dead Isolated Skin.*—Since the water lost through dead skin is lost through diffusion and not through secretion by the sweat glands, it became of interest to study the rate of loss of water through

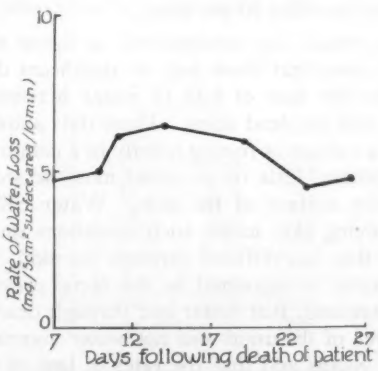


Fig. 4.—The rate of loss of water in the dead skin of the epigastrium obtained from a patient at autopsy. The values on the abscissa indicate time in days between the death of the patient and the taking of each measurement.

living and through dead skin simultaneously in order to learn the amount of water secreted by sweat glands during life. Measurements were made on the epigastrium of a living subject resting quietly in a comfortable environment; simultaneously an equal area of 2 or 3 different dead skins was measured. The temperature of

the skin of the epigastrium was determined with thermocouples, and the temperature of the dead skins in the saline baths was brought to within 1 degree C. (1.8 degrees F.) of that of the living skin and was held at that level. Skins of 5 living subjects resting quietly in bed and 7 dead skins obtained at autopsy from 7 different subjects were studied in this way. The skins had been

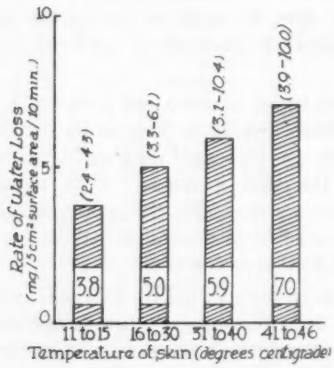


Fig. 5.—The influence of the temperature of dead skin on the rate of loss of water through the skin.

dead from several hours to about two weeks and had been stored as described in the previous experiments. Several measurements were made at each sitting and were then repeated on other days. The room containing the living subjects was comfortable (temperature 75 F. [38 C.] and relative humidity 50 per cent).

The results are summarized in figure 6. It can be seen that there was no significant difference in the rate of loss of water between the living and the dead skins. These data show that when a subject is resting quietly in a comfortable environment little or no sweat must be secreted onto the surface of the skin. Water collected from living skin under such conditions must be water that has diffused through the skin. This conclusion is supported by the facts, previously demonstrated, that water lost through dead skin is water of diffusion and not water secreted by sweat glands and that the rates of loss of water from the surface of dead and of living skin are the same.

*Experiment 5: An Attempt to Allow Sweat to Accumulate on the Surface of Living Skin of Subjects Resting Quietly in a Comfortable Environment.*—If no sweat is secreted onto the surface of the skin with the living subject resting in a comfortable environment, after a period of time there should be no accumulation of sweat in the chambers covering the areas of skin.

Living subjects rested quietly in bed with the temperature and relative humidity 75 F. (38 C.) and 50 per cent respectively. The rate of loss of water from the skin over ten minute intervals was measured; then all flow of oxygen through the chamber covering the areas of skin was stopped for periods varying from ten to sixty minutes. The water that had accumulated during that time was collected, and 7 separate groups of measurements, on different subjects and different specimens of dead skin, were made.

The results are summarized by figure 7. It can be seen that there was no accumulation of sweat after any of the periods allowed for accumulation. There was a slight difference between the amount of water collected during a ten minute period before allowing for the accumulation of sweat and after doing so. This difference was the same, essentially 1.5 mg., whether the period allowed for accumulation of sweat was ten minutes or sixty minutes. If sweat had been accumulating, the quantity that accumulated should have increased as the time allowed for accumulation increased. Such was not the case.

The constant difference of about 1.5 mg. is most probably due to the fact that the dry oxygen which was circulated over the skin to pick up the water tended to dry the skin a little too much, and with cessation of the flow of oxygen the skin was remoistened by the diffusion of water from the underlying tissues. After the atmosphere of the brass chambers on the skin became saturated with moisture, diffusion of water through the skin stopped.

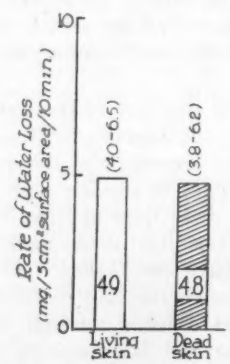


Fig. 6.—The rate of loss of water through dead skin of the epigastrium and through skin of the epigastrium of living subjects resting quietly in bed in a comfortable environment.

These experiments further substantiate the view that the water collected from the skin of a subject resting quietly in a comfortable environment is water of diffusion and not water secreted by the underlying sweat glands.

*Experiment 6: The Rate of Loss of Water from the Surface of the Cover of a Large Blister as Compared with that from Living and Dead Skin.*—In 4 living subjects blisters of about 10 sq. cm. in area were raised with cantharides plasters (see "Materials and Methods"). The rate of loss of water in each subject was measured

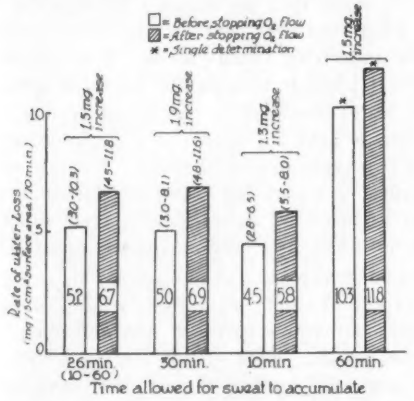


Fig. 7.—The rate of loss of water through living skin before and after allowing for the accumulation of water in the brass chambers isolating the areas of skin. Seven groups of studies were conducted except for the last determination represented in the figure. The measurements are summarized by the first group of figures.

simultaneously from the surface of the cover of the blister and from an equal area of normal skin adjacent to the blister. The conditions of the experiments were the same as described for the preceding experiments. The subjects rested quietly in bed in a comfortable environment. Blisters were raised on 7 different subjects. Approximately ten hours was required to raise the blisters and about ten hours for the slight inflammatory reaction to subside so that the measurements could be made.

The results are shown in figure 8. It can be seen that there was no significant difference between the rate of loss of water through the intact normal living skin and that from the surface of the cover of a blister in the epigastric area. For example, the individual values of the loss of water in 4 simultaneous measurements were as follows: from the normal areas of skin, 5.0, 5.1, 3.0 and 8.1 mg. respectively per 5 sq. cm. of surface area per ten minutes, and from the covers of the blisters, 4.8, 4.3, 3.0 and 6.0 mg. respectively. It can also be seen that the rates of loss of water from the normal skin and from the surface of the blisters were about the same as those from dead skin.

Separation of the superficial layers of epidermis from the underlying structures insured a separation of the terminal portions of the sweat ducts from the underlying functioning glomeruli of the sweat glands and made it impossible for sweat to be poured onto the surface of the skin. Furthermore, since the water lost from the surface of the cover of a blister was the same in amount as that lost from the adjacent living normal skin and from dead skin, the data further substantiate the view that in a subject resting quietly in a comfortable environment the water lost through the skin is lost by diffusion and not by secretion of the sweat glands. The roles of the various layers of the epidermis in conserving water are presented in detail in another publication.[5]

*Experiment 7: The Rate of Loss of Water from the Surface of the Skin in Two Subjects with Severe Atrophy of the Sweat Glands.*—Since patients with ectodermal dysplasia with complete absence of sweat glands were not available for study, 2 subjects with marked atrophy of the sweat glands were studied in an attempt to learn the relative roles of sweat glands and diffusion in the rate of loss of water through the skin. Both of these patients complained of an inability to sweat and suffered considerably from the summer heat. On biopsy the skins showed extremely atrophic sweat glands and a great reduction in the number of sweat glands. The cause for the atrophy could not be determined. One patient was a white woman 49 years of age

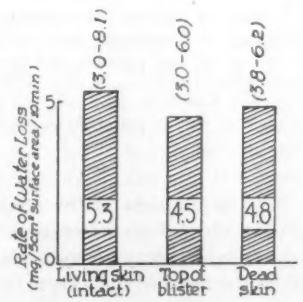


Fig. 8.—The rate of loss of water through the cover of a blister and through adjacent living intact skin of the epigastrium of 7 human subjects. The rate of loss of water through dead skin is also shown for the purpose of comparison.

and the other a Negro man of 61. The rate of loss of water was determined for areas of skin of the epigastric region in a comfortable environment (temperature 75 F. [38 C.] and relative

5. Winsor, T., and Burch, G. E.: Differential Roles of Layers of Human Epigastric Skin on Diffusion Rate of Water, Anch. Int. Med., this issue, p. 428.

humidity 50 per cent) and also in a hot and humid one (temperature 115 F. [60 C.] and relative humidity 80 per cent). The hot and humid environment was used in order to stimulate sweating and to determine the maximum sweating capacity of the glands of the skin of the epigastrium.

The results are summarized in figure 9. The rate of loss of water through the skins with atrophic glands was essentially the same as that through dead skin. When the temperature and humidity of the room were increased the rate of loss of water through the skin with atrophic sweat glands was the same as for dead skin under similar conditions of temperature. Normal epigastric skin showed marked sweating (fig. 9) when the subject was in a hot and humid environment [3b] while the skin of the subjects with atrophic glands showed an increase in the rate of loss of water which was no more than would be expected on the basis of the effects of temperature on the rate of diffusion.

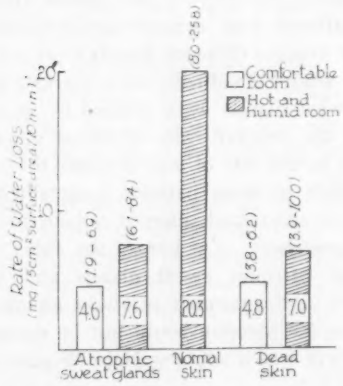


Fig. 9.—The rate of loss of water through the skin of the epigastrium of 2 patients with atrophic skin, through the skin of normal subjects and through dead skin in a comfortable environment (75 F. [38 C.] and 50 per cent relative humidity) and in a hot and humid environment (115 F. [60 C.] and 80 per cent relative humidity).

These data indicate a lack of function of the atrophic sweat glands of the 2 patients. The loss of water through their skins took place by diffusion and was increased by increasing the environmental temperature to the extent expected for effects of temperature on the rate of diffusion through skin. Since the rate of loss of water through normal skin of subjects in a comfortable environment and through skin with functionless sweat glands were the same, the data support the conclusion that loss of water through the skin of a subject in a comfortable environment is water of diffusion and not water secreted by underlying sweat glands.

## COMMENT

These studies tend to show that the water lost from the surface of the skin of human subjects resting quietly in a comfortable environment is water that has diffused through the skin and most probably contains no water secreted by the underlying sweat glands. This conclusion makes it possible to separate water of diffusion from water secreted by the sweat glands, thus opening a field for study of the physiology of these two types of loss of water. Because of the difficulty of separating water of diffusion from water secreted by sweat glands, their functions have not previously been adequately observed.

Pinson,[6] using a method similar in many respects to that employed in these studies, obtained results comparable to those just described. He inactivated the sweat glands with a solution of formaldehyde, forcing the solution cataphoretically to the functioning portions of the sweat glands. Pinson showed that the glands so treated were physiologically inactive and that the loss of water through the skin treated with formaldehyde was no different from that through normal untreated skin at similar temperatures below 34 C.

Since it is possible to separate these waters of the skin, it is necessary for the sake of clarity and specificity to redefine perspiration. Perspiration has been distinguished as either insensible or sensible. The former type is defined as "those gaseous emanations from the body which do not appear in the form of sensible sweat or moisture, such as gaseous productions arising from the lungs in exhalation and from the skin by vaporization." The latter type is defined as "perspiration which appears as moisture on the skin."[7] Obviously such terms are scarcely applicable to water lost through the skin. It is not suggested that these terms be discarded, but it is necessary that new ones be added. The term diffusion water might be used to indicate water that has diffused through the skin; sweat would indicate the secretions of the sweat glands. It is evident that the water of diffusion is the major part of the water lost insensibly through the skin of resting, comfortable normal subjects.

6 Pinson, E. A.: Evaporation from Human Skin with Sweat Glands Inactivated, Am. J. Physiol. **137**: 492, 1942.

7. Dorland, W. A. N.: The American Illustrated Medical Dictionary, ed. 19, Philadelphia, W. B. Saunders Company, 1943.

The present studies were limited to the skin of the epigastrium, but judging from previous observations [8] of loss of water from other portions of the skin, it is quite likely that the behavior of the skin of other areas is essentially the same under the conditions of the experiments described. It is possible, however, that nervous sweating would interfere with studies on the palms, the soles and the axillas. Sweating may be profuse in a subject emotionally disturbed, even though the temperature and relative humidity of the environment are within the levels of comfort. There is no reason to believe, however, that diffusion of water through the skin of these areas is very different from that through the skin of the epigastrium, although the thick epidermis of the palmar and plantar surfaces may influence the rate of diffusion.

The observations on the dead skins are of interest from several aspects. The fact that the rate of loss of water by diffusion through the skin after death was virtually the same as in the living subject and did not vary even after three weeks of storage in a refrigerator with recurrent periods of freezing and thawing tends to support the view that diffusion of water through the skin is a purely physical process. If the living processes of the skin were very important in influencing diffusion of water through the skin definite differences should have been noted between living and dead skin. Furthermore, there was no significant difference between diffusion of water through skin, whether the skin was studied within three hours of death or after four weeks. The dead skins were kept in a frozen state when not under observation. These findings indicate strongly that the structures of the skin which limit diffusion of water are hardy and might possibly be associated in large part with the keratinized layer of the skin, which undergoes spontaneous autolysis relatively slowly. This hypothesis will be discussed in more detail in another publication.[5]

The rates of diffusion of water through Negro and white dead skins were the same. This suggests that the pigment of the skin is not a factor influencing diffusion of water. It is evident that any variations between the races in their ability to become acclimatized to subtropical or tropical climates cannot be explained by a difference in the rate of diffusion of water through their skins.

Figure 7 is of particular interest. It can be seen from this figure that the amount of water accumulated on the skin enclosed for study by the brass chambers was fairly constant, about 1.5 mg. The same quantity of water accumulated whether an interval of ten minutes or one of sixty minutes was allowed for accumulation. This is most plausibly explained by the studies of Büttner [9] and his associates, who found a limiting or transposition zone 6 mm. thick enveloping the surface of the human body in a room free from air currents. This zone is saturated with water vapor. A similar zone was probably formed over the skin enclosed by the brass chambers. When the flow of the dry oxygen was stopped the superficial layers of the skin probably became slightly moistened, and the internal atmosphere of the chambers sealed to the skin became saturated with water vapor. The amount of water necessary to bring this about should be fairly constant, and the water must diffuse through the skin in less than ten minutes. Once the level of saturation is reached there should be no further accumulation, regardless of the length of time allowed, for the pressure gradient of diffusion is 0.[6]

It is well to point out that the method used in this study favors a maximum rate of diffusion of water through the skin, for dry oxygen was flowing fairly rapidly over the skin. It is unlikely that the rates just recorded are approached in subjects resting quietly in a comfortable environment free from air currents. This view is supported by other studies [10] in which it was noted that subjects resting quietly in a comfortable environment free from air currents lost little if any weight insensibly through the skin in short periods. The influence of air currents, the temperature of the skin, the relative humidity of the surrounding atmosphere and the electrolyte and protein states of the tissue fluids are among the many factors which influence the rate of diffusion of water through skin. Some of these have been studied.[6]

## SUMMARY

The water that escapes through the skin of a subject resting quietly in a comfortable environment is water that has diffused through the skin and not water that is secreted by the underlying sweat glands. A method is described by means of which diffusion water and sweat actively secreted can be measured quantitatively.

8. Burch, G. E.; Cohn, A. E., and Neumann, C.: A Study of the Rate of Water Loss from the Surfaces of the Fingertips and Toetips of Normal and Senile Subjects and Patients with Arterial Hypertension, Am. Heart J. **23**:185, 1942. Neumann, Cohn and Burch.[2] Burch and Sodeman.[3b]

9. Büttner, K.: Physikalisches zum Warmehaushalt des Menschen, Klin. Wchnschr. **11**:1508, 1932.

10. Burch, G. E., and Winsor, T.: The Relation of Insensible Loss of Weight to Water Loss from the Lungs, Am. J. M. Sc., to be published.

The rate of diffusion of water through dead and through living skin is virtually the same. The rate is about the same through skin studied within a few hours and through skin studied several days after the death of the subject.

It is suggested that the terms insensible and sensible perspiration are not specific enough and that the terms diffusion water and sweat should be employed, the former to indicate water that traverses the skin wholly by diffusion and the latter to indicate water secreted by sweat glands, regardless of whether or not it is visible. The terms insensible and sensible perspiration are not necessarily to be discarded, although they tend to be confusing and nonspecific.

G. Morgavi contributed considerably to these studies.

# DIABETES AND TUBERCULOSIS

ANDREW L. BANYAI, M.D.
WAUWATOSA, WIS.
AND
ANTHONY V. CADDEN, M.D.
MILWAUKEE

The significance of the association of diabetes and tuberculosis is accentuated by two circumstances: (1) the continued rise in the frequency of diabetes and (2) the increase in the incidence of pulmonary tuberculosis in persons with diabetes in spite of the sustained prewar decline in the tuberculosis mortality rate in the general population. Relative to the association of diabetes and tuberculosis the available reports show a striking difference between European and American data.

TABLE 1.—*Incidence of Tuberculosis in Diabetes: Reports of European Clinicians*

| Author | Diabetic Patients: Total | With Pulmonary Tuberculosis: No. | With Pulmonary Tuberculosis: % |
|---|---|---|---|
| Abraham, A.: Med. Klin. **23**: 720, 1927 | 360 | 35 | 9.7 |
| Rosenberg, M., and Wolf, G.: Klin. Wchnschr. **6**: 936, 1927 | 1,000 | 40 | 4.0 |
| Boller, R.: Beitr. z. Klin. d. Tuberk. **85**: 173, 1934 | 1,441 | 116 | 10.1 |
| Rathery, F.: Marie, J., and Roy L.: Rev. de méd., Paris **54**: 107, 1937 | 750 | 124 | 16.5 |
| Vrhovac, V.: Liječn. vjes. **59**: 130 and 205, 1937 | 840 | 84 | 10.0 |
| Bokretas, A.: Tuberkulozis **1**: 13, 1938 | 550 | 33 | 6.0 |
| Pilgerstorfer [34] (1938) | 1,208 | 71 | 5.9 |
| Himsworth, N. P.: Quart. J. Med. **7**: 373, 1938 | 230 | 15 | 6.5 |
| Total | 6,379 | 518 | 8.1 |

If the tuberculosis morbidity rate is calculated by multiplying the mortality rate by 10, as suggested by Krause,[1] the average tuberculosis mortality rate from 1927 to 1938, inclusive, corresponding to the period covered by the reports of the American authors presented in table 2, was 64 per 100,000. This indicates a morbidity rate of 0.6 per cent. When this figure is compared with the average incidence given in table 2, it appears that tuberculosis occurs four times as frequently in diabetic persons as in the general population of the United States. The investigations of Root [2] revealed the importance of considering the age of the diabetic patient relative to the frequency of tuberculosis as a complication.

TABLE 2.—*Incidence of Tuberculosis in Diabetes: Reports of American Clinicians*

| Author | Diabetic Patients: Total | With Pulmonary Tuberculosis: No. | With Pulmonary Tuberculosis: % |
|---|---|---|---|
| Golden, R., in discussion on Sosman and Steidl | 1,091 | 51 | 4.6 |
| Sosman, M. C., and Steidl, J. H.: Am. J. Roentgenol. **17**: 625, 1927 | 182 | 17 | 9.3 |
| Wilder, R. M., and Adams, S. F.: Proc. Staff Meet., Mayo Clin. **4**: 192, 1929 | 1,000 | 10 | 1.0 |
| Fritz, R.: Am. J. M. Sc. **180**: 192, 1930 | 1,529 | 35 | 2.3 |
| Wendt, L. F., and Peck, F. B.: Am. J. M. Sc. **181**: 52, 1931 | 1,073 | 42 | 3.9 |
| Severinghaus, E. L.: Am. J. M. Sec. **182**: 311, 1931 | 500 | 8 | 1.6 |
| Murphy, F. D., and Moxon, G. F.: Am. J. M. Sc. **182**: 301, 1931 | 827 | 40 | 4.8 |
| Kramer, L. I., and Lawson, H. A.: Ann. Int. Med. **6**: 1426, 1933 | 408 | 5 | 1.2 |
| Joslin [43] (1934) | 9,592 | 245 | 2.5 |
| Ralli and Steinberg [50] (1938) | 748 | 33 | 4.3 |
| Total | 16,950 | 486 | 2.8 |

He found that the reinfection type of pulmonary tuberculosis was more than thirteen times as frequent in children who acquired diabetes before the age of 15 years as among Massachusetts school children and sixteen times as frequent in adolescent diabetic patients in whom the disease developed between the ages of 15.1 and 19.9 years as in the corresponding group of high school students.

A number of theories have been proposed concerning the cause of predisposition of diabetic persons to tuberculosis. The idea that is most

From the Muirdale Sanatorium and from the Department of Medicine, Marquette University Medical School.

1. Krause, A. K., in Nelson Loose Leaf Living Medicine, New York, Thos. Nelson & Sons, 1920, vol. 1, p. 309.

2. Root, H. F.: Association of Diabetes and Tuberculosis, New England J. Med. **210**:1, 78, 127 and 192, 1934; Diabetic Control Versus Caloric Sufficiency in the Treatment of Diabetes and Pulmonary Tuberculosis, Am. J. M. Sc. **200**:53, 1940.

readily offered is that hyperglycemia favors the growth of tubercle bacilli in the body. In a recent reference to the statement of Tolstoi relative to the permissibility of glycosuria in diabetes, Joslin and his associates stated that hyperglycemia implies a high percentage of sugar in the tissues and that, directly or indirectly, the latter conduces to lack of normal repair of tissue and resistance to infection.[3] However, the experimental studies of Richardson [4] and Pillsbury and Kulchar [5] proved that the increased sugar content of the blood and tissues is not a causative factor in lowering the resistance of the body or in aiding the propagation of infectious microorganisms in the tissues. The observations of Hirsch-Kauffmann and Heimann-Trosin [6] revealed no acceleration of bacterial growth in the blood of diabetic patients containing as high as 410 mg. of dextrose per hundred cubic centimeters. According to Keeton,[7] the predisposition to infection is explainable by a local tissue acidosis with its disturbed electrolyte balance which interferes with the water transport. Grafe [8] cited da Costa and Beardly, who observed that the opsonic index in persons with severe diabetes is lower than normal. Also, the studies of Moen and Reimann [9] indicated a lowering of the opsonic index, of the production of complement and antibody and of the bacteriostatic capacity of the blood in diabetic patients. Although the qualitative and quantitative decrease of these entities points toward a diminished potential immunologic response, these observations do not offer any clue as to the ultimate cause and process of development of these phenomena.

Long [10] expressed the opinion that the cause of predisposition may lie in the diabetic patients' disordered fat metabolism through an increased availability of glycerin, which is one of the best nutrients for acid-fast micro-organisms. Root [2] pointed out that the growth of tubercle bacilli in the body depends on chemical factors, such as accessibility of substances for nutrition, reaction and oxygen tension of the tissues, water relations and other, so far unexplored, factors. The fact that diabetic coma and uncontrolled diabetes were followed frequently by a flare-up of the tuberculous process was thought to be partly attributable to an oversupply of nitrogenous compounds that help to support the growth of tubercle bacilli. Hirsch-Kauffmann and Heimann-Trosin [6] demonstrated that blood from children in diabetic coma promoted bacterial growth. Furthermore, Root [2] emphasized the possible importance of changes in the reticuloendothelial system. It is known that interference with the normal function of this system causes a decrease in the defense and resistance of the body against infection. In persons with diabetes the reticuloendothelial cells are sometimes found to be distended with fat, especially when diabetes is relatively uncontrolled; consequently their normal defensive function is lowered. Keeton's [7] conception that the appearance of acidosis destroys the resistance of the tissues and favors the spread of the tuberculous process is in line with the experience of Smithburn,[11] who demonstrated in his experimental studies that one can increase the virulence of the tubercle bacilli by increasing the acidity of the culture medium. The impaired resistance of diabetic persons to infection, according to Moolten,[12] is a part of the general vulnerability of the diabetic tissues to injury of any type and is attributed to deficient cellular oxidation. An important contribution to this problem is the report of Geyelin,[13] who found that the incidence of tuberculosis is less when the diabetic patients are being treated with high carbohydrate diet.

From the study of the available clinical and experimental investigations one gains the impression that the role of vitamin A may explain

3. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: Treatment of Diabetes, J. A. M. A. **115**:1038 (Sept. 21) 1940.

4. Richardson, R.: Immunity in Diabetes: I. Influence of Diabetes on the Development of Antibacterial Properties in the Blood, J. Clin. Investigation **12**:1143, 1933; II. Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine, ibid. **14**:389, 1935.

5. Pillsbury, D. M., and Kulchar, G. V.: Relation of Experimental Skin Infection to Carbohydrate Metabolism: Effect of Hypertonic Glucose and Sodium Chloride Solution Injected Intraperitoneally, Am. J. M. Sc. **190**:169, 1935.

6. Hirsch-Kauffmann, H., and Heimann-Trosin, A.: Bacterial Growth in the Blood of Diabetic Children, Klin. Wchnschr. **5**:1922, 1926.

7. Keeton, R. W., cited by Rest, A.: Tuberculosis in Jewish Diabetics, Am. Rev. Tuberc. **43**:344, 1941; Diabetes and Tuberculosis, in Goldberg, B.: Clinical Tuberulosis, Philadelphia, F. A. Davis Company, 1935.

8. Grafe, E.: Metabolic Diseases and Their Treatment, Philadelphia, Lea & Febiger, 1933.

9. Moen, J. K., and Reimann, H. A.: Immune Reactions in Diabetes, Arch. Int. Med. **51**:789 (May) 1933.

10. Long, E. R.: A Chemical View of the Pathogenesis of Tuberculosis, Am. Rev. Tuberc. **22**:467, 1930.

11. Smithburn, K. C.: The Colony Morphology of Tubercle Bacilli, Nat. Tuberc. A. Tr. **31**:161, 1935.

12. Moolten, S. E.: Pulmonary Infection and Necrosis in Diabetes Mellitus, Arch. Int. Med. **66**:561 (Sept.) 1940.

13. Geyelin, H. R.: Recent Studies on Diabetes in Children, Atlantic M. J. **29**:829, 1926; The Treatment of Diabetes with Insulin (After Ten Years), J. A. M. A. **104**:1203 (April 6) 1935.

in a large measure the increased susceptibility of diabetic patients to tuberculosis. Vitamin A deficiency causes specific pathologic changes in the mucosa of the respiratory system. These consist of atrophy of the epithelium with associated disappearance of the ciliary function, proliferation of the basal cells and replacement of the original epithelium by a stratified keratinizing epithelium. Bessey and Wolbach [14] stated that in the lungs of human infants as well as of experimental animals these changes lead to the occlusion of bronchi, formation and filling of bronchiectatic cavities with keratinized cells and atelectasis; the plugs of desquamated epithelial cells act as a culture medium for pathogenic micro-organisms. They assumed that the frequency of pneumonia in infants may be explained on the basis of vitamin A deficiency as one of the underlying causes. The pneumonia is invited by the atrophy of the mucosa that precedes the appearance of keratinizing epithelium; the pneumonia is usually of the interstitial and peribronchial type. Wilson and Dubois [15] made pathologic studies of a fatal case of nutritional keratomalacia in an infant and noted an extensive keratinization of the bronchial epithelium, bronchiectatic cavities and abscesses. Pneumonia was the immediate cause of death in 2 of 4 patients of Ross [16] in whom keratomalacia was diagnosed during life. Of 86 children with xerophthalmia observed by Bloch [17] pneumonia was detected in 15 and bronchitis in 12.

The occurrence of vitamin A deficiency in diabetes was reported in the recent medical literature. Brazer and Curtis [18] observed 20 patients with juvenile diabetes mellitus and found evidence of hypovitaminosis A in all of them. Freston and Loughlin [19] studied a group of juvenile diabetic patients and found that 71 per cent of the ones with poorly controlled diabetes and 48 per cent of those whose disease was excellently controlled had low values for vitamin A. Schroeder [20] ascertained that carotene as well as vitamin A disappeared from the blood during diabetic coma. Ralli, Brandaleone and Mandelbaum [21] maintained that in persons with diabetes the apparent cause of hypovitaminosis A is the inability of the liver to convert carotene to vitamin A. Normally 95 per cent of the vitamin A content of the body is stored in the liver. Its metabolism, as was pointed out by Schneider and Widman,[22] is closely coupled with the glycogen metabolism of the liver. It is known that in uncontrolled diabetes the glycogen disappears from its normal depots in this organ. This circumstance, then, explains the low vitamin A values found in the liver of diabetic patients and also the consequent clinically demonstrable hypovitaminosis A.

It was stated in the May 1940 issue of the "Statistical Bulletin of the Metropolitan Life Insurance Company" that there were at that time 500,000 to 600,000 persons with diabetes in the United States, and it was estimated that the number will reach 1,000,000 by the end of the present decade. In view of the high number of diabetic persons and the relatively great frequency of tuberculosis as a complication of this disease, it is surprising to find only a small number of diabetic patients admitted to tuberculosis sanatoriums. In 1919 Landis, Funk and Montgomery [23] reviewed 31,834 sanatorium admissions of patients treated for pulmonary tuberculosis in twenty-nine institutions. They found a coexistence of these two diseases in between 0.33 and 0.17 per cent. In 1929 Tompkins [24] analyzed the cases of 4,500 persons admitted with tuberculosis to one of the United States Veterans' Hospitals and reported the simultaneous occurrence of diabetes in 0.31 per cent. In 1931, at the time of the publication of our first report on this subject,[25] there had been 3,963 new patients admitted to Muirdale Sanatorium during the preceding eight year period. Of these there were 31, or 0.7 per cent, who had diabetes. During

14. Bessey, O. A., and Wolbach, S. B.: Vitamin A: Physiology and Pathology, J. A. M. A. **110**:2072 (June 18) 1938.

15. Wilson, J. R., and DuBois, R. O.: Report of a Fatal Case of Keratomalacia in an Infant with Postmortem Examination, Am. J. Dis. Child. **26**:431 (Nov.) 1923.

16. Ross, S. G.: Nutritional Keratomalacia in Infants, with Reports of Four Cases, Am. J. Dis. Child. **22**:232 (Sept.) 1921.

17. Bloch, C. E.: Effects of Deficiency in Vitamins in Infancy, Am. J. Dis. Child. **42**:263 (Aug.) 1931.

18. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, Arch. Int. Med. **65**:90 (Jan.) 1940.

19. Freston, J. M., and Loughlin, W. C.: Vitamin Deficiencies in Diabetic Children, New York State J. Med. **42**:1833, 1942.

20. Schroeder, H.: Relation of Most Important Vitamins to Carbohydrate Metabolism, Ztschr. f. d. ges. exper. Med. **101**:373, 1937.

21. Ralli, E. P.; Brandaleone, H., and Mandelbaum, T.: Studies on the Effect of the Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus, J. Lab. & Clin. Med. **20**:1266, 1935.

22. Schneider, E., and Widman, E.: The Relationship Between Vitamin A, Provitamin A, and Liver Damage and Resistance to Infection, Klin. Wchnschr. **13**: 1497, 1934.

23. Landis, H. R. M.; Funk, E. H., and Montgomery, C. M.: Treatment of Diabetes Complicating Pulmonary Tuberculosis, Am. Rev. Tuberc. **2**:690, 1919.

24. Tompkins, R. D.: Diabetes and Tuberculosis, South. M. J. **22**:143, 1929.

25. Banyai, A. L.: Diabetes and Pulmonary Tuberculosis, Am. Rev. Tuberc. **24**:650, 1931.

the subsequent thirteen years, covered by the present study, there were 94, or 1.6 per cent, with diabetes out of 5,575 new admissions. If it is assumed that about the same percentage prevails in other tuberculosis sanatoriums throughout the country, it becomes evident immediately that the number of diabetic patients treated in tuberculosis institutions is far less than the estimated number of patients who have diabetes and tuberculosis.

Failure to hospitalize these patients in specialized institutions carries serious implications from the standpoint of the patient's welfare as well as from the standpoint of public health. In a search for reasons of this failure, the following points seemed to be obvious: (1) lack of diagnostic consciousness; (2) improper interpretation of symptoms and signs referable to the respiratory tract; (3) incomplete diagnostic investigation, and (4) asymptomatic forms of pulmonary tuberculosis. The much higher percentage of recovery of persons with early than with advanced pulmonary tuberculosis justifies a plea for an early diagnosis of this condition in diabetic patients. Experience has shown that the best attitude is to anticipate the possibility of tuberculosis as a complication. We are of the opinion that all diabetic patients should be given a tuberculin test; the test should be repeated annually on persons with negative reactions to tuberculin; a roentgenogram of the chest should be taken at least once a year for all persons with positive reactions; examination of the sputum for tubercle bacilli should be made on all patients who have a productive cough; if the roentgenogram of the chest reveals conditions characteristic of or suggestive of pulmonary tuberculosis and the patient is unable to produce a satisfactory specimen of sputum, the fasting stomach contents should be aspirated on five successive occasions and examined for tubercle bacilli by culture or by inoculation of guinea pigs.

Unless the physician who is treating diabetic patients has a high index of diagnostic suspicion relative to tuberculosis and unless he avails himself of the most efficient methods of diagnosis, numerous instances of early and curable tuberculosis will be missed. This point is well illustrated by the fact that of the 125 diabetic patients admitted to Muirdale Sanatorium between Jan. 1, 1923 and Dec. 31, 1943 there were only 3, or 2.4 per cent, classified as having minimal tuberculosis. As a glaring contrast, 104, or 83.2 per cent, of the diabetic patients were admitted in the far advanced stage of tuberculosis. According to available information and our own experience, this percentage of persons with minimal tuberculosis is lower and that of persons with far advanced tuberculosis is substantially higher than corresponding figures pertaining to general sanatorium admissions.

There was a great deal of emphasis placed in earlier publications on the lack of subjective symptoms and the apparent well-being of diabetic patients with active pulmonary tuberculosis. The following presumable factors were cited as being responsible for this apparent paradox: (1) acidosis; (2) anatomic pathologic changes due to advanced age; (3) dehydration, and (4) decreased pyrogenic activity in diabetes. It was assumed that constitutional symptoms, such as chills, fever and malaise, were due to allergic reactions of the body and consequently were mitigated by acidosis that may ensue during the course of diabetes. In advanced age the lymphatics of the lung, with concomitant atrophy of the lymphatics throughout the body, become less permeable; therefore it was thought that they may represent a barrier against the massive absorption and transportation of toxins. Also it was pointed out that febrile reactions are not as common in old age as in the earlier age periods, possibly because of an insufficient transmission of peripheral stimuli to the thermoregulatory center or because of the diminished irritability of this center. Some authors attributed the infrequency of night sweats to dehydration. The absence of fever in some diabetic patients with extensive pulmonary lesions was considered to be due to a tendency to hypothermia and a diminished pyrogenic activity in diabetes. In contrast to this conception, data presented in table 3 show the frequency with which localizing and constitutional symptoms occurred in our 125 patients with diabetes and tuberculosis. These figures closely parallel those found for nondiabetic tuberculous patients with the same extent of the pulmonary disease. On the other hand, the examination of contacts and the results of mass roentgen ray surveys, conducted in connection

TABLE 3.—*Distribution According to the Stage of Pulmonary Tuberculosis in Various Age Groups*

| Age, Years | Stage of Pulmonary Tuberculosis | | | Total | |
|---|---|---|---|---|---|
| | Minimal | Moderately Advanced | Far Advanced | Number | Per Cent |
| Less than 20.... | .. | 1 | 4 | 5 | 4.0 |
| 20 to 39..... | .. | 6 | 26 | 32 | 25.6 |
| 40 to 59..... | 2 | 9 | 54 | 65 | 52.0 |
| 60 and over..... | 1 | 2 | 20 | 23 | 18.4 |
| Total..... | 3 = 2.4% | 18 = 14.4% | 104 = 83.2% | 125 | 100.0 |

with preinduction and preemployment examinations, have revealed ample proof of the existence of asymptomatic tuberculosis in nondiabetic persons. In view of this evidence, the conception of asymptomatic tuberculosis as a characteristic complication of diabetes must be discarded.

On the basis of clinical observations the type of pulmonary disease was classified in our 125 patients as follows: (1) productive lesions in 4 (3.2 per cent); (2) productive-exudative lesions in 13 (10.4 per cent); (3) exudative lesions in 25 (20.0 per cent), and (4) caseous and fibrocaseous lesions in 83 (66.4 per cent). Similar observations have been recorded by other authors. The presence of cavities, varying from honeycombing to large solitary or multiple cavities, was observed in 89 patients (71.2 per cent) in our series. In an earlier publication, Mueller [26] commented on the frequency of cavities in his diabetic patients who had pulmonary tuberculosis. Myers and McKean [27] noted cavitation in 90 per cent of their patients. In general, complications were less frequently seen than in nondiabetic patients, with the exception of spontaneous pneumothorax which occurred in 8 patients (6.4 per cent). Also, Wiener and Kavee [28] noted this complication in 4.1 per cent of their patients. Their studies at necropsy revealed that fibrous adhesions between the visceral and the parietal pleura are twice as frequent in nondiabetic as in diabetic patients. This circumstance—together with the tendency of tuberculous lesions to caseation and destruction of tissue—may well explain the high incidence of spontaneous pneumothorax in the latter group.

TABLE 4.—*Distribution of Patients with Various Stages of Pulmonary Tuberculosis According to Race and Sex*

| Classification | Stage of Pulmonary Tuberculosis: Minimal | Moderately Advanced | Far Advanced | Total: Number | Total: Per Cent |
|---|---|---|---|---|---|
| White | 3 | 16 | 99 | 118 | 94.4 |
| Negro | .. | 1 | 4 | 5 | 0.4 |
| Others | .. | 1 | 1 | 2 | 0.2 |
| Male | 2 | 15 | 62 | 79 | 63.2 |
| Female | 1 | 3 | 42 | 46 | 36.8 |

The immunobiologic response of the body to tuberculosis during diabetes has been the subject of careful studies. The review of our data shows that the tuberculin reaction, as an index of the allergic status of the patient, manifests the same variability as seen in patients with tuberculosis without diabetes. Thirteen and eight-tenths per cent of the tuberculin reactions were classified as slight, 48.2 per cent as average and 37.9 per cent as strongly positive. An analysis of the total white blood cell count, the differential white cell count and the monocyte-lymphocyte ratio revealed no characteristic changes in this group of patients. In some of the earlier publications on this subject, attention was called to the fact that the sedimentation rate of the erythrocytes is out of proportion to the extent of the tuberculous lesion and is only slightly increased in persons with tuberculosis associated with diabetes. An analysis of our records revealed that in this group only 2 patients had normal sedimentation rates in association with active pulmonary tuberculosis. This is in line with observations we

TABLE 5.—*Symptoms of Tuberculous Diabetic Patients on Admission to the Sanatorium*

| Symptoms | Stage of Pulmonary Tuberculosis: Minimal | | Moderately Advanced | | Far Advanced | | Total No. of Patients with Symptoms | |
|---|---|---|---|---|---|---|---|---|
| Number of patients admitted | 3 | | 18 | | 104 | | | |
| | Number | Per Cent | Number | Per Cent | Number | Per Cent | Number | Per Cent |
| Cough | 3 | 100.0 | 17 | 94.4 | 101 | 97.1 | 121 | 96.8 |
| Expectoration | 2 | 66.6 | 14 | 77.7 | 100 | 96.1 | 116 | 92.6 |
| Pulmonary hemorrhage | | | | | | | | |
| Slight | 1 | 33.3 | 5 | 27.7 | 29 | 28.8 | .. | .... |
| Moderate | 1 | 33.3 | 1 | 5.5 | 8 | 7.6 | 51 | 40.8 |
| Severe | .. | .... | .. | .... | 6 | 5.7 | .. | .... |
| Thoracic pain | 1 | 33.3 | 6 | 33.3 | 46 | 44.2 | 53 | 42.4 |
| Dyspnea | 1 | 33.3 | 3 | 16.6 | 66 | 63.4 | 70 | 56.0 |
| Chills | .. | .... | 4 | 22.2 | 27 | 25.9 | 31 | 24.8 |
| Fever | .. | .... | 7 | 38.8 | 58 | 55.7 | 65 | 52.0 |
| Night sweats | 1 | 33.3 | 8 | 44.4 | 48 | 46.1 | 57 | 45.6 |
| Malaise | 3 | 100.0 | 12 | 66.6 | 87 | 83.6 | 102 | 81.6 |
| Loss of appetite | 1 | 33.3 | 4 | 22.2 | 57 | 54.7 | 62 | 49.6 |
| Loss of weight | 3 | 100.0 | 12 | 66.6 | 94 | 90.3 | 109 | 87.1 |

26. Mueller, E. M.: Relationship Between Diabetes and Pulmonary and Intestinal Tuberculosis, Ztschr. f. Tuberk. **80**:281, 1938.

27. Myers, G. B., and McKean, R. M.: Diabetes and Tuberculosis, Am. Rev. Tuberc. **32**:65, 1935.

28. Wiener, J. J., and Kavee, J.: Pulmonary Tuberculosis and Diabetes Mellitus, Am. Rev. Tuberc. **34**: 179, 1936.

reported previously.[29] Our protocols relative to this question and covering 9,914 tuberculous patients showed that approximately 8 per cent of them had normal sinking velocity of the erythrocytes. Simultaneous occurrence of active tuberculosis and a normal sedimentation rate was observed in all age groups and in patients with primary infection as well as in patients with a reinfection type of disease. The erythrocyte sedimentation rate does not parallel the type and extent of tuberculosis. Normal rates were encountered in association with minimal, moderately advanced and far advanced disease, with productive and with exudative pulmonary tuberculosis and with solitary and with multiple cavities. Sputum containing tubercle bacilli examined directly or after homogenization was found in association with a normal sedimentation rate.

The scarcity of tubercle bacilli in the sputum of tuberculous diabetic patients was often reported in earlier studies. It was thought that this was caused by the overgrowth of other bacteria. This conception, however, does not hold true according to more recent investigations. In our previous series of 31 patients, tubercle bacilli were detectable in the sputum examined directly or by homogenization in all but 4. In the present series, with the aid of improved technic, tubercle bacilli were readily found even in a higher percentage of cases. Insufficient or unacceptable specimens of sputum necessitated a search for tubercle bacilli in the fasting gastric contents in 7.4 per cent of the patients.

The management of diabetes in tuberculous patients has evolved along the same line of changes that has characterized the general trend in the treatment of this disease. The practice of keeping these persons on a low carbohydrate diet has been gradually abandoned. As early as 1931 Kutschera-Aichbergen[30] advocated the administration of high carbohydrate diet and insulin. Keeton[7] summarized the advantages of increasing the carbohydrate intake of diabetic persons with tuberculosis as follows: 1. The appetite of these patients is often poor and must be tempted. 2. Some of the patients tolerate fat poorly, and diarrhea easily develops. 3. They often have ketosis due to infection; this can be counterbalanced by a high carbohydrate intake. 4. Carbohydrates help the conservation of protein and thus aid the maintenance of nitrogen balance. 5. High carbohydrate intake may lessen the incidence of arteriosclerosis. Similarly, Duncan[31] endorsed a diet that represents 34 to 45 calories per kilogram of body weight and contains liberal amounts of carbohydrates, from 200 to 300 Gm. a day. Bertram[32] considered a high carbohydrate diet advantageous because (1) it tends to preserve glycogen in the tissues, (2) it prevents hypercholesterolemia and (3) it mitigates hyperepinephrinemia that follows injections of insulin. Melzer[33] imposed little restriction on the carbohydrate intake of his patients, but, instead, he used large doses of insulin whenever it was necessary for maintaining a normal blood sugar level and for avoiding glycosuria. According to Root,[2] the standard diet of diabetic patients with tuberculosis should contain 150 Gm. of carbohydrate, 80 Gm. of protein and 100 Gm. of fat; a diet to increase weight should include 250 Gm. of carbohydrate, 87 Gm. of protein and 110 to 120 Gm. of fat. The pertinent observations of Pilgerstorfer[34] are of interest. He found that the duration of life of diabetic patients with tuberculosis who were kept on a low carbohydrate diet was three fourths of one year as against three and one-fourth years for patients kept on a high carbohydrate intake. The recent report of Greene and Swanson[35] brought added support in favor of the latter type of diet. They pointed out that there is a greater demand for dextrose during an infection with or without systemic reaction and unless the carbohydrate content of the diet is increased the sugar stores of the body will be reduced in proportion to the increased demand. Furthermore, they emphasized that in such cases the addition of extra carbohydrate to the diet either will not increase the insulin requirement or will make any increase in requirement due to infection comparatively less than would be necessary without added sugar; the patient thereby utilizes a greater amount of dextrose with less insulin.

In addition to these data and earlier favorable reports on the utilization of higher carbohydrate diets without added insulin by several clinicians,

29. Banyai, A. L., and Anderson, S. V.: Erythrocyte Sedimentation Test in Tuberculosis, Arch. Int. Med. **46**:787 (Nov.) 1930. Banyai, A. L., and Caldwell, E.: Normal Sedimentation Rate in Open Tuberculosis, Am. Rev. Tuberc. **38**:491, 1938. Banyai, A. L., and Cadden, A. V.: Limitations of the Erythrocyte Sedimentation Test in Tuberculosis, Arch. Int. Med. **72**:245 (Aug.) 1943.

30. Kutschera-Aichbergen, H.: Tuberculosis and Diabetes, Wien. klin. Wchnschr. **44**:1217, 1931.

31. Duncan, G. G.: Diseases of Metabolism, Philadelphia, W. B. Saunders Company, 1942.

32. Bertram, F.: Zuckerkrankheit, Leipzig, Georg Thieme, 1934.

33. Melzer, E.: Diet and Insulin in Diabetes Complicated by Pulmonary Tuberculosis, Deutsches Tuberk.-Bl. **11**:161, 1937.

34. Pilgerstorfer, W.: Pulmonary Tuberculosis in Diabetes, Wien. Arch. f. inn. Med. **32**:7, 1938.

35. Greene, J. A., and Swanson, L. W.: Utilization and Effect of Added Dextrose in Cases of Controlled and Uncontrolled Diabetes, J. A. M. A. **118**:364 (Jan. 31) 1942.

we wish to discuss the potential value of this diet from the standpoint of vitamin A metabolism. Reference has been made to the effect of hypovitaminosis A on the mucous membrane of the respiratory tract and to the occurrence of vitamin A deficiency in diabetes. The apparent cause of the latter seems to be the inability of the liver to convert carotene to vitamin A. Also, it has been mentioned that the metabolism of vitamin A is closely coupled with the glycogen metabolism of the liver. Mirsky and his associates [36] found that diabetic adults do not retain carbohydrate in their liver to the same degree as do normal adults. Furthermore, it is known that in persons with uncontrolled diabetes the glycogen disappears from its normal depots in this organ. If the premise is tenable that glycogen serves to maintain the hepatic parenchyma and makes possible its regeneration, that glycogen is essential for the protection of the functional integrity of the liver, it must be conceded that a high carbohydrate diet that is capable of maintaining glycogen reserve in this organ is a proper measure in the management of diabetes. When diabetes is complicated by active tuberculosis, one has to consider the presence of infection as an added factor that calls for a liberal carbohydrate diet. Soskin [37] stated that in normal states there is no amylase activity in the liver but under abnormal conditions amylase may assume an important role in the breakdown of glycogen. He found that livers removed from animals intoxicated with diphtheria toxin exhibited significant amylase activity within the hepatic cells; amylase splits glycogen into maltose, which, in turn, is transformed into two molecules of dextrose by maltase: this may explain in part the low levels of liver glycogen in infection and toxemia. Rabuchin [38] observed that there was an increase in the amylase content of the blood of tuberculous patients. He also found in his experimental work that the glycogen content of the liver was low in guinea pigs and rabbits that were inoculated with tubercle bacilli and subsequently died of tuberculosis. Ritzmann [39] postulated that the epinephrine-dextrose curve is proportional to the glycogen content of the liver. According to this conception a flat curve in advanced tuberculosis may be taken as suggestive of low level of glycogen in the liver. Richardson [40] reported that in both normal rabbits and depancreatized cats survival after intravenous inoculation with bacteria was increased by high carbohydrate diets which raised the glycogen content of the liver.

On the basis of their investigations and of preceding studies of others, Bridge and Winter [41] emphasized that the major aspect of the disturbance of the carbohydrate metabolism in diabetes is centered in the liver; that the removal of this organ from diabetic dogs causes a rapid disappearance of diabetic symptoms, and that insulin appears to influence carbohydrate combustion in diabetes only indirectly, this influence apparently being associated with changes in the glycogen content of the liver. This conception implies the need for restoring or preserving the normal glycogen content of the liver by high carbohydrate intake that will enhance the action of the therapeutically given insulin.

The studies of Mirsky [36] demonstrated clearly that an excessive intake of carbohydrate is not an etiologic factor in the development of acidosis in diabetic patients and that the sudden development of an excessive blood sugar level in consequence of high carbohydrate intake does not facilitate or precipitate acidosis or coma and, therefore, that from this point of view hyperglycemia is not dangerous.

If the patients are unable to metabolize adequate amounts of sugar on a well planned diet, insulin is administered. Earlier writers reported on the possible occurrence of focal reactions in tuberculous lungs and consequent pulmonary hemorrhages following the use of insulin. Subsequent extensive clinical observations, including our own, have firmly established the fact that insulin does not cause focal reaction and its use in this respect is perfectly safe. If one keeps in mind the importance of the normal glycogen content of the liver for the functional integrity of this organ, it is significant that insulin increases the protoplasmal glycogen in the liver, as revealed by the studies of Bornstein.[42] Fur-

36. Mirsky, I. A.; Korenberg, M.; Nelson, N., and Nelson, W. E.: Hepatic Glycogen Reserves in Diabetes Mellitus, Endocrinology **28**:358, 1941. Mirsky, I. A.: Etiology of Diabetic Acidosis, J. A. M. A. **118**: 690 (Feb. 28) 1942.

37. Soskin, S.: Storage and Significance of Tissue Glycogen in Health and Disease, Arch. Int. Med. **71**: 219 (Feb.) 1943.

38. Rabuchin, I. E.: Carbohydrate Metabolism in Experimental Tuberculosis and Pulmonary Tuberculosis, Beitr. z. Klin. d. Tuberk. **74**:541, 1930.

39. Ritzmann, H.: The Mechanism of Adrenalin-Glycosuria, Arch. f. exper. Path. u. Pharmakol. **61**:231, 1909.

40. Richardson, R.: Immunity in Diabetes: Relation of Tissue Glycogen and Blood Chemistry to Bacterial Dissemination, Antibody Formation and Survival After Infection in Diabetes, J. Clin. Investigation **19**:239, 1940.

41. Bridge, E. M., and Winter, E. A.: Diabetes, Insulin Action and Respiratory Quotient, Bull. Johns Hopkins Hosp. **64**:257 1939.

42. Bornstein, S.: Glycogen in the Liver and Kidneys in Diabetic Patients Treated with Insulin, Ztschr. f. d. ges. exper. Med. **66**:623, 1929.

thermore, insulin has an antiketogenic action in that by normalizing hepatic function it obviates the formation of acetone. The dosage of insulin is often hard to manage for persons with tuberculosis because of the capricious appetite and the variable amounts of food ingested and because of the effect of toxins that decrease the carbohydrate tolerance by their depressing action on the islands of Langerhans. The latter may be observed as the result of unsuspected spread of the disease in the lungs or of the development of complications, such as pleurisy with effusion, tuberculous peritonitis and tuberculosis of bone. Reactions to insulin are no more frequent in tuberculous diabetic patients than in diabetic patients without tuberculosis. The previously reported presumably inherent hypersensitiveness can be readily explained on the basis of inadequate ingestion or absorption of carbohydrate due to various causes, including evident or latent intestinal tuberculosis. On the other hand, elevation of the renal threshold in older persons may cause an apparent increase in carbohydrate tolerance. Joslin [43] observed increases in carbohydrate tolerance when diabetic tuberculous patients' pulmonary disease approached the terminal stage. He mentioned that diabetes, even of the severest grade, may practically disappear when this phase of tuberculosis is reached. The theory of Lundberg that the apparent favorable effect of advanced forms of tuberculosis is due to the production of an insulin-like substance (parainsulin) in the tuberculous tissue has not been corroborated. It is more reasonable to think that the increased carbohydrate tolerance is attributable to the progressive loss of weight and emaciation.

Mosenthal and Mark [44] made a thorough study of the value of protamine zinc insulin and regular insulin. Their report indicated that the clinical course of tuberculosis is distinctly more favorable with protamine zinc insulin than with unmodified, or regular, insulin. We have used protamine zinc insulin in our practice since its general clinical adoption. In some instances, we have found it expedient to combine it with regular insulin. We have noted repeatedly that the amount of insulin used could be substantially reduced with the disappearance of exudative lesions.

One of the most important problems in the management of diabetes in tuberculous patients is the standard to accept for the control of diabetes as the most salutary one for both of these diseases. Is it preferable to adhere to earlier orthodox methods and attempt to keep the urine free of sugar and maintain a normal blood sugar level, or is it therapeutically justifiable to permit glycosuria and tolerate hyperglycemia? Tolstoi,[45] discussing the treatment of uncomplicated diabetes, referred to his observations on 84 patients that he carried out in association with Weber. The patients were receiving a diet of 75 Gm. of protein, 60 Gm. of fat and 200 Gm. of carbohydrate and protamine zinc insulin in daily doses up to 50 units. Glycosuria and hyperglycemia were disregarded in the management of these patients provided (1) the weight could be maintained, (2) ketone bodies were absent from the urine and (3) freedom of the following symptoms was assured: thirst, polyuria, frequency of urination, hunger, weakness and fatigue, polyphagia, pruritus limited to the genitalia and visual disturbances. The great majority of their patients on this regimen maintained their weight, and many of them gained; none presented any of these symptoms, and only 1 had acetonuria. This practice is based on the concept of Cori [46] that in diabetes a high blood sugar level is necessary for any sugar to be utilized in the body tissues; it is strengthened by the observations of Bridge and Winter,[41] who demonstrated that in an insulin-treated diabetic person carbohydrate is utilized in the presence of hyperglycemia and associated glycosuria. Tolstoi and Weber [45] expressed the opinion that if with the aid of insulin diabetic patients utilize quantities of carbohydrate sufficient for their metabolic requirements the excess of sugar may be excreted without damaging consequences.

This method of treating diabetes was severely criticized by Joslin and his associates.[3] They expressed the conviction that it is necessary to control the hyperglycemia of diabetes (1) because it is an abnormal state, (2) because a high blood sugar level is a constant stimulus for secretion of insulin and allows no opportunity for recuperation of the pancreas and (3) because control of hyperglycemia and glycosuria proves utilization of the diet. They stated that "unhesitatingly we maintain that the blood sugar should approach normal because it is an index of the control of the diabetic condition; if normal, it is one as-

43. Joslin, E. P., cited by Root, H. F.: Association of Diabetes and Tuberculosis, New England J. Med. **210**:1, 1934; Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928.

44. Mosenthal, H. O., and Mark, M. F.: Advantages of Protamine Zinc Insulin, J. A. M. A. **116**:2652 (June 14) 1941.

45. Tolstoi, E.: Conferences on Therapy: Management of Diabetic Emergencies, J. A. M. A. **115**:454 (Aug. 10) 1940. Tolstoi, E., and Weber, F. C., Jr.: Protamine Zinc Insulin: Clinical Study; Report of Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year, Arch. Int. Med. **66**: 670 (Sept.) 1940.

46. Cori, C. F.: Mammalian Carbohydrate Metabolism, Physiotherapy Rev. **11**:143, 1931.

surance that the whole disease is being treated well."

Between these diametrically opposing opinions stands the attitude of other clinicians that was well formulated by Mosenthal.[47] He said that hyperglycemia without glycosuria not only has no damaging effect on the heart and other tissues but is a necessary stimulus for the proper assimilation and oxidation of dextrose. Furthermore, he stated that hyperglycemia associated with glycosuria, polyuria and dehydration is responsible for most of the serious complications of diabetes. Cori [46] found that glycogen can be stored in the liver only when the blood sugar level is increased. Wirtschafter [48] advised adjustment of the diet and the insulin of the diabetic patient so that a slight trace of glycosuria is maintained throughout the day, whereby the possibility of hypoglycemia consistently is avoided. The serious consequences of hypoglycemia are well known. The functional integrity of the liver, including the production and storage of normal amounts of vitamin A, is greatly influenced by hypoglycemia in that, as Cori [46] pointed out, during periods of hypoglycemia glycogen is always removed from the liver. This is brought about, according to the observations of Somogyi,[49] by increased glycogenolysis that, in turn, leads to hyperglycemia and glycosuria. His warning against overdoses of insulin which cause periods of hypoglycemia is well epitomized in the axiom, "Hypoglycemia begets hyperglycemia."

With the previously discussed phenomena in mind, one can readily appreciate that in the treatment of tuberculous diabetic patients restoring and maintaining the normal physiologic status of the liver are of cardinal importance. We have found that in patients who were given a well planned diet and adequate amounts of insulin slight glycosuria and hyperglycemia not exceeding 200 mg. per hundred cubic centimeters are compatible with favorable therapeutic response as far as pulmonary tuberculosis is concerned. It is possible that the satisfactory results encountered in this group were due to the avoidance of hypoglycemia, with its serious consequences. Improvement in the pulmonary condition of patients belonging to this group compares favorably with that recorded for tuberculous patients whose blood sugar was kept on a practically normal level.

Relative to the management of diabetes complicated by tuberculosis, Ralli and Steinberg [50] recommended four meals in twenty-four hours for the reason that the usual three meals leave the patient with no outside source of energy for fourteen hours and thereby lead to a depletion of the available body stores. The fourth meal, in the evening, provides for optimal absorption of dextrose during the night, and thus nocturnal reactions to protamine zinc insulin are obviated. Also they called attention to the liability of diabetic patients to become readily dehydrated, and they recommended ample fluid intake and about 6 Gm. of sodium chloride as such daily. The clinical investigations of Fenz [51] led him to the conclusion that diabetic diarrheas are gastrogenic in origin; they are due to anacidity or hypoacidity. This type of diarrhea occurred in nearly 38 per cent of his diabetic patients. He noted achlorhydria in 56.3 per cent and hypochlorhydria in 17.2 per cent of 116 unselected diabetic persons. The correction of this condition is essential for maintenance of normal intestinal absorption. For the same reason, in the presence of moderately advanced and far advanced pulmonary tuberculosis one must anticipate intestinal tuberculosis, and when it is found one should treat it early and effectively. Although it may appear heretical in the treatment of tuberculosis, we are of the opinion that reducing the diet for overweight diabetic patients with pulmonary tuberculosis is as justifiable and practicable as for nontuberculous obese persons with diabetes. Root [2] advised that, in general, insulin should rarely if ever be omitted for diabetic children with pulmonary tuberculosis with the exception of emaciated children in the terminal stage of the disease.

Because of the multiple intrinsic factors that may adversely influence the carbohydrate metabolism in tuberculous patients whenever insulin is being used, one must be aware of the possibility of hypoglycemic reactions, characterized by sudden weakness, tremor, perspiration, palpitation, nervous irritability, blurred vision, diplopia, intense hunger and convulsions. In some instances hypoglycemia is indicated by slight or moderate headache on waking in the morning. At times, hypoglycemic blood sugar levels may be present without any apparent symptoms. It was emphasized by Sindoni [52] that such a hypo-

47. Mosenthal, H. O.: Hyperglycemia, J. A. M. A. **105**:484 (Aug. 17) 1935.

48. Wirtschafter, Z. T.: Blood Sugar Versus Urinary Sugar, J. A. M. A. **113**:1752 (Nov. 4) 1939.

49. Somogyi, M.: Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals, Proc. Soc. Exper. Biol. & Med. **38**:51, 1938.

50. Ralli, E. P., and Steinberg, I.: Incidence of Tuberculosis in a New York City Diabetic Clinic, J. Lab. & Clin. Med. **23**:581, 1938.

51. Fenz, E.: Anacidity of Diabetic Patients, Wien. Arch. f. inn. Med. **32**:283, 1938.

52. Sindoni, A.: Blood Sugar Versus Urinary Sugar, J. A. M. A. **112**:2503 (June 17); 2595 (June 24) 1939.

glycemic state, escaping detection by urinary examination alone and allowed to continue at frequent intervals for an indefinite period, may prove to have serious consequences. Root [2] pointed out that the calcium content of the diet is of special importance in diabetes because in diabetic patients a negative calcium balance is bound to develop in the presence of acidosis or diarrhea.

The occurrence of hypovitaminosis A in diabetes has been previously mentioned. In another paper, detailed discussion is presented concerning the occurrence of hypovitaminosis A in tuberculosis.[53] Briefly it may be stated that there is experimental and clinical evidence that tuberculosis has an untoward effect on the glycogen metabolism of the liver and consequently on the vitamin A storage and exchange that are closely associated with the glycogen balance of this organ. Dietary increase in the carotene (provitamin A) intake is not likely to be of value for correcting hypovitaminosis A because of the hepatopancreatic dysfunction in diabetes mellitus. Functional derangement of the intestinal absorption of vitamin A in tuberculosis reduces considerably the effectiveness of the generally prescribed doses of vitamin A. For these reasons we are of the opinion that the administration of massive doses of vitamin A, from 150,000 to 200,000 U. S. P. units daily, may serve as a useful adjunct in the management of diabetes mellitus complicated by pulmonary tuberculosis.

The indications and contraindications for collapse therapy are the same for diabetic as for nondiabetic patients. Because in persons with predominantly exudative and caseous tuberculous lesions of recent origin the production of artificial pneumothorax is often followed by pleural effusion and empyema or by spontaneous pneumothorax, the use of this measure is rather restricted for persons with diabetes who not infrequently are admitted to the sanatorium with extensive caseous tuberculosis. The limitation of the applicability of pneumothorax in these patients undoubtedly has a bearing on the ultimate prognosis. On the other hand, patients who tolerate artificial pneumothorax well are eligible for ambulatory treatment outside the sanatorium on the basis of the same criteria that govern the selection for ambulatory treatment of nondiabetic persons with artificial pneumothorax.

The controversial status of the question of prognosis of tuberculosis in diabetic patients was discussed in detail in our previous communication (1931). Reports dealing with this problem and published since this date have continued to present greatly divergent opinions. Rathery and Rudolf [54] stated that the course of tuberculosis is not influenced in any definite way by diabetes. Delijannis and Petassis [55] found that if the diabetes responds to diet and insulin and the patients' urine is kept free of sugar their chances for recovery are little affected by the diabetes. Dunlop [56] expressed the view that with early diagnosis of the tuberculosis and efficient treatment of the diabetes the latter will have no adverse influence on the tuberculous process. Epstein and Trubowitz [57] observed 46 patients over 40 years of age who had both diabetes and pulmonary tuberculosis and who were treated by artificial pneumothorax. Conversion of the sputum from positive to negative was higher than in the nondiabetic control group. McKean and his associates [58] concluded from their observations that the presence of controlled diabetes does not alter the prognosis of pulmonary tuberculosis and that the mortality of associated diabetes and tuberculosis parallels closely that of pulmonary tuberculosis alone. This is in harmony with the opinions expressed by Joslin,[48] Mark and his associates [59] and Duncan.[31]

On the other hand, Kutschera-Aichbergen [30] noted that even with proper diet and adequate doses of insulin diabetic persons with tuberculosis do poorly. Lorenzen [60] found that in patients with exudative lesions diet and insulin did not prevent a downward course. The life expectancy was rather short, except when the diabetes was mild or the tuberculous process was productive. Keeton [7] expressed the opinion that with early diagnosis and appropriate treatment of tuberculosis and with accurate control of the diabetes these patients have a fair expectancy of life but this expectancy is not so good as for

53. Banyai, A. L., and Cadden, A. V.: The Rationale of the Administration of Massive Doses of Vitamin A in Tuberculous Diabetics, Dis. of Chest **10**:133, 1944.

54. Rathery, F., and Rudolf, M.: Les maladies de la nutrition, Paris méd. **1**:405, 1931.

55. Delijannis, G., and Petassis, G.: Clinical Experience in Insulin-Treated Tuberculous Diabetics, Wien. klin. Wchnschr. **45**:909, 1932.

56. Dunlop, D. M.: Diabetes and Tuberculosis, Edinburgh M. J. **44**:351, 1937.

57. Epstein, H. H., and Trubowitz, S.: Pneumothorax in the Diabetic Past the Age of Forty, Quart. Bull., Sea View Hosp. **6**:309, 1941.

58. McKean, R. M.; Thosteson, G. C., and Brooks, N.: Treatment of Tuberculosis and Diabetes, Am. Rev. Tuberc. **43**:31, 1941.

59. Mark, M. F.; Mosenthal, H. O., and Liu, F.: Diabetes Mellitus and Tuberculosis, Am. J. M. Sc. **203**:490, 1942.

60. Lorenzen, J. N.: Combination of Diabetes and Pulmonary Tuberculosis, Acta tuberc. Scandinav. **5**: 265, 1931.

nondiabetic tuberculous patients. Fett [61] estimated that the life expectancy of patients with associated diabetes and tuberculosis is reduced to one half of that of patients with tuberculosis without diabetes. Jeanneret [62] claimed that tuberculosis is more invasive even in well controlled diabetes. Benjamin and Verghese [63] reported that in diabetic patients with far advanced pulmonary tuberculosis good therapeutic results were observed less often than in nondiabetic patients with the same extent of tuberculosis.

Our records show that of the 115 discharged diabetic tuberculous patients, 96 had far advanced pulmonary tuberculosis on admission. Of these, 14 (14.6 per cent) were classified on discharge as having the tuberculosis apparently arrested, quiescent or improved; 21 (21.9 per cent) were classified as having unimproved tuberculosis and 61 (63.5 per cent) died during their stay in the sanatorium. It can be seen that the treatment of tuberculosis failed entirely in 85.4 per cent of this group of patients. In the group with moderately advanced tuberculosis the disease of 47 per cent of the patients became apparently arrested, quiescent or improved, and 52.9 per cent of the patients remained unimproved or died. The therapeutic results in both groups are lower than those recorded for nondiabetic patients with far advanced and moderately advanced pulmonary tuberculosis. We are of the opinion that these less favorable results can be attributed (1) to the lowered resistance, defense and repair of the diabetic tissues relative to the tuberculous process and its spread; (2) to the frequency of predominantly exudative lesions with a pronounced tendency to destruction of tissue and excavation (this type of lesion obviates the effective use of artificial pneumothorax because of the danger of the easily provoked complicating empyema), and (3) to complications, such as arteriosclerosis, nephritis, coronary obstruction and myocardial degeneration, which are observed in diabetic patients and in patients in the last few decades of life—a higher percentage of diabetic than of nondiabetic tuberculous patients belong to these age groups.

TABLE 6.—*Prognosis for 115 Discharged Diabetic Patients According to Stage of Tuberculosis*

| Stage of Tuberculosis on Admission | Classification on Discharge | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Apparently Arrested | | Quiescent | | Improved | | Unimproved | | Died | | Total | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Minimal | 1 | 50.0 | .. | .... | 1 | 50.0 | .. | .... | .. | .... | 2 | 1.7 |
| Moderately advanced | 3 | 17.6 | 2 | 11.8 | 3 | 17.6 | 3 | 17.6 | 6 | 35.3 | 17 | 14.8 |
| Far advanced | 4 | 4.1 | 4 | 4.1 | 6 | 6.3 | 21 | 21.9 | 61 | 63.5 | 96 | 83.5 |
| Total | 8 | 6.9 | 6 | 5.2 | 10 | 8.7 | 24 | 20.9 | 67 | 58.2 | 115 | 100.0 |

## CONCLUSIONS

An analysis of the reports of ten American clinicians based on the observations of 17,358 cases of diabetes indicates a higher incidence of tuberculosis in diabetic persons than in the general population of the United States.

It is reasonable to believe that the increased susceptibility of diabetic patients to tuberculosis is due to a complexity of causes. On the basis of available clinical and experimental data we are of the opinion that hypovitaminosis A may have a significant role in this respect.

The number of patients with diabetes and pulmonary tuberculosis treated in specialized institutions is far below the estimated number of tuberculous diabetic persons.

The fact that an unusually high percentage of diabetic patients who acquire tuberculosis are not adequately treated for their pulmonary disease before it reaches the far advanced stage calls for an urgent revision of the diagnostic approach to this problem.

The conception that asymptomatic tuberculosis is a characteristic complication of diabetes is untenable. This type of pulmonary tuberculosis has been often found in roentgen ray surveys of nondiabetic persons.

For the recognition of early tuberculosis it is necessary to anticipate this disease. 1. All diabetic patients should be tested with tuberculin and the test should be repeated periodically on all patients with negative reactions to tuberculin. 2. A roentgenogram of the chest should be taken for all patients with positive reactions at least once a year. 3. Adequate search for tubercle bacilli should be carried out when sputum is available or when roentgenologic observations justify repeated aspirations of the fasting gastric contents.

61. Fett, A.: Pulmonary Tuberculosis and Diabetes, Ztschr. f. Tuberk. **82**:113, 1939.

62. Jeanneret, R.: Section of Adhesions and Collapse Therapy in Pulmonary Tuberculosis and Diabetes, Schweiz. med. Wchnschr. **70**:531, 1940.

63. Benjamin, P. V., and Verghese, M. C.: Pulmonary Tuberculosis and Diabetes Mellitus, Indian M. Gaz. **75**:588, 1940.

We have found that in tuberculous diabetic patients who were given a well planned diet and adequate amounts of insulin slight glycosuria and hyperglycemia not exceeding 200 mg. per hundred cubic centimeters are compatible with favorable therapeutic response as far as pulmonary tuberculosis is concerned. The results in this group of patients compare favorably with those recorded for tuberculous patients whose blood sugar was maintained on practically a normal level.

The indications and contraindications for pulmonary collapse therapy are the same for diabetic as for nondiabetic tuberculous patients. Because of the frequency with which empyema complicates artificial pneumothorax in persons with predominantly exudative recent tuberculous lesions, the use of this measure is greatly limited for tuberculous diabetic patients.

During the period covered by this study 115 tuberculous diabetic patients were discharged from Muirdale Sanatorium. On discharge 47 per cent of the persons with moderately advanced pulmonary tuberculosis were classified as having the disease apparently arrested, quiescent or improved, and 52.9 per cent were unimproved or had died. Of the far advanced group 14.5 per cent reached the stage where their disease was apparently arrested, quiescent or improved, while 85.4 per cent remained unimproved or died. These therapeutic results are less favorable than those recorded for nondiabetic patients with moderately advanced and far advanced pulmonary tuberculosis.

# Progress in Internal Medicine

## SYPHILIS

### REVIEW OF THE RECENT LITERATURE

CHARLES F. MOHR, M.D.; VIRGIL SCOTT, M.D.; RICHARD D. HAHN, M.D.; E. GURNEY CLARK, M.D., AND JOSEPH EARLE MOORE, M.D.
BALTIMORE

*(Concluded from Page 411)*

### UNTOWARD EFFECTS OF TREATMENT

*Arsenical Encephalopathy.*—Since the advent of more intensive methods of treating early syphilis, a steadily increasing interest is evident in arsenical encephalopathy. This has resulted in more cases being reported, as well as investigations to determine the exact nature of the lesions.

Scheinker [67] has had an opportunity to study 5 cases of encephalopathy due to arsphenamine, in all of which hemorrhages and typical vascular alterations were predominant. The vascular lesions were similar to those previously described in cases of injury to the brain and spinal cord under the heading "central vasoparalysis."

The author suggests the following theory of pathogenesis:

> The main vascular alterations observed in all cases of encephalopathy caused by arsphenamine correspond to those lesions described under the heading of central vasoparalysis. These vascular lesions occur as a result of the presence of an acute physical or chemical irritant, and trauma seems to be the most frequent etiologic factor. . . . After a contraction of the blood vessel wall of short duration there soon occurs a definite paralytic dilatation of the exposed vessel. This is usually associated with stasis; an apparent slowing of the blood stream occurs. If the circulation is impaired because of stasis, a local accumulation of carbon dioxide would result and hence further vascular dilatation. The retarded circulation would no doubt interfere with the adequate supply of oxygenated blood to smaller veins and capillaries. If these alterations are sufficiently severe degeneration of the vessel wall may occur. The vessel wall would become more permeable for serous fluid and red blood cells. The resulting extravasation of large masses of red cells into the tremendously distended perivascular spaces with blood would serve in turn further to retard the circulation and contribute to the hypoxia of the nerve tissue. There is no doubt that these changes would interfere with proper exchange of oxygen and carbon dioxide so that the metabolism of the tissue would be more and more disturbed and finally incompatible with the maintenance of the normal function. This would lead to pericapillary necrosis of tissue, the different forms and stages of which have been described.

Scheinker concurs that the term hemorrhagic encephalitis be abandoned, since the lesions of the brain are not inflammatory, as the term "encephalitis" implies. The condition might better be called encephalopathy due to arsphenamine.

Young and Gordon [68] report 6 cases of acute encephalopathy which occurred in the course of 10,000 injections of neoarsphenamine given by a scheme which provided two injections of 0.6 Gm. of neoarsphenamine and two of a bismuth compound (0.1 Gm. of bismuth metal) each week. The 5 fatal cases showed a striking conformity as to pattern: onset with an epileptiform attack twelve to forty-eight hours after the third to the fifth injection and death in twenty-four to forty-eight hours. One patient did not have a convulsion; 1 patient had fever from the first injection, and all had some degree of fever before the last injection was received. There is no information concerning the number of patients treated. Necropsies showed congestion and petechial hemorrhages of the brain.

In an effort to foretell the development of toxic encephalopathy before onset of clinical symptoms, Kalz and Steeves [69] have studied the blood prothrombin concentration in 15 patients undergoing intensive arsenotherapy, including 1 infant with congenital syphilis who died while under study. A marked reduction of prothrombin concentration occurred in every instance during five days of massive arsenotherapy. In 8 patients there was a reduction of prothrombin concentration to levels below 20 per cent of normal, which is in the range of spontaneous hemorrhage. In the 1 patient who died, the infant with congenital syphilis, the blood prothrombin concentration fell below 20 per cent of normal shortly before death. This patient, having received a total of 300 mg. of mapharsen by intravenous drip during a five day interval without untoward reaction other than vomiting and fever on the second day, died suddenly two days after

67. Scheinker, I. M.: Genesis of Encephalopathy Due to Arsphenamine (Central Vasoparalysis Due to Arsphenamine), Arch. Path. **37**:91 (Feb.) 1944.

68. Young, W. A., and Gordon, S.: Acute Encephalopathy During Neoarsphenamine Treatment, Brit. J. Ven. Dis. **20**:34 (March) 1944.

69. Kalz, F., and Steeves, L. C.: Decrease of Prothrombin Concentration in Massive Arsenotherapy: A Preliminary Report, Am. J. Syph., Gonor. & Ven. Dis. **28**:89 (Jan.) 1944.

therapy ceased. This was the only instance in which a continuing fall in prothrombin concentration was observed after termination of therapy. Necropsy showed little of significance other than edema and vascular congestion of the brain.

*Postarsphenamine Jaundice.*—We are not aware of an appreciable increase in the incidence of postarsenical jaundice in the United States. However, there seems to be an unexplained rise in the number of cases of this condition reported in England.

Marshall [70] says that during a two year period, 1940 and 1941, he has observed 600 cases of jaundice. These are many more than ordinarily occur over a similar period. About half of the patients were syphilitic persons seen in the Eastern Command and London district (Woolwich, Colchester and London Military Isolation Hospital); the others were nonsyphilitic. Of 940 patients under treatment for syphilis, most of whom received neoarsphenamine, 29 per cent became jaundiced. No comparable rates for nonsyphilitic persons can be obtained, but the types of hepatitis were essentially the same in the two groups (mild acute hepatitis, chronic hepatitis, subacute yellow atrophy and acute yellow atrophy). The fact that hepatitis, with or without jaundice, may occur at any stage of acquired or congenital syphilis and the factor of arsenic treatment contribute to the predominance of the illness in persons with syphilis. Treatment with bismuth, and in a few cases with arsenic, was continued throughout the illness without incident. There were slight rises in serum phosphates and cholesterol. Only 4 patients became jaundiced again after resumption of arsenotherapy three months after the first attack. In 80 per cent of the cases jaundice occurred about the beginning of the second course of arsenical therapy. The type and lot of neoarsphenamine could not be incriminated. There was no localization to certain areas; there was less jaundice among civilians than soldiers, and less among air force personnel than army; no seasonal variation could be demonstrated; no evidence of droplet spread was apparent; closely associated groups showed jaundice at the same time; alcohol as a factor could not be assessed; the soldiers had a better diet but a higher jaundice rate than civilians; men seemed more liable to have jaundice than women; and there was no difference according to stage of the syphilitic infection.

Among 1,659 patients with syphilis under treatment in Scotland, jaundice developed in 171 (10.3 per cent); there were 2 fatalities. Anderson [71] was unable to obtain evidence of any such incidence among nonsyphilitic persons. There must be much subclinical infective jaundice, he thinks, and since impairment of hepatic function can be shown to exist as long as two years after an attack of catarrhal jaundice, such persons are more susceptible to infective agents or toxic materials. Toxicity, sensitization or diet may play a part. Studies by means of van den Bergh tests, and determinations of plasma phosphatase and cholesterol contributed no clearcut dividing line between "arsenical" jaundice and jaundice resulting from other toxic or infective causes. An attempt to estimate the liver's ability to stand up to treatment by means of Quick's method of oral administration of 6 Gm. of sodium benzoate and subsequent estimation of the hippuric acid excretion gave the author the "feeling" that a reading below 3 Gm. during treatment is an indication for caution. Synchronized estimations of plasma proteins showed no departure from normal. The author ends with an encouraging statement—there is more jaundice in Germany too!

The technic of hepatic biopsy was used to study 35 cases of postarsenical jaundice and in addition cases of ordinary epidemic hepatitis and the jaundice which follows infusions of serum. Dible and McMichael [72] found a wide range of histologic appearances but these were common to each group and the resemblance was close. Both a diffuse and a zonal form of hepatic damage are described, the latter with more intense destruction of parts of the lobule. Regular lobular structure was preserved. Hemorrhage into the central parts of the lobule and the fatty degeneration commonly seen in arsenical hepatitis produced in animals were conspicuously absent. No lesions which could be called gummatous or syphilitic were seen. The liver of 1 patient with florid secondary syphilis was subjected to biopsy and was passed as normal. The authors point out that since the pathologic picture was similar in all respects to that in epidemic and serum-produced jaundice and that since jaundice is produced in animals only after massive dosage of an arsenical (fifteen times the human dose), this work does not support the suggestion that either syphilitic lesions of the liver or arsenical poisoning plays a part in the development of postarsenical jaundice.

70. Marshall, J.: Jaundice in Syphilitics, Brit. J. Ven. Dis. **19**:52 (June) 1943.

71. Anderson, T. E.: Jaundice in Syphilitics, Brit. J. Ven. Dis. **19**:58 (June) 1943.

72. Dible, J. H., and McMichael, J.: The Pathology of Arsenotherapy, Brit. J. Ven. Dis. **19**:102 (Sept.) 1943.

Maclagan [73] employed a modification of Gray's (1940) colloidal gold reaction of the serum as a test of hepatic function. The modification consists of the introduction of a barbitone (diethyl barbituric acid) buffer solution which permits the test to be performed in a single tube in a reproducible manner without preliminary standardization of the gold sol. The results obtained in 200 jaundiced and 200 nonjaundiced patients suggest that the test is a valuable indicator of hepatic damage. The almost uniformly negative results in obstructive jaundice give the test a particular value in distinguishing this condition from infective hepatitis or hepatic cirrhosis. Of particular interest are the results in infective hepatitis and arsenical jaundice. The serum of 95 per cent of 105 patients with infective hepatitis gave a positive colloidal gold reaction, as contrasted with only 40 per cent positive reactions in 35 patients with arsenical jaundice. These results suggest some essential pathologic difference in the two groups.

In a not too convincing report, Beattie and Marshall [74] attempt to explain the increased incidence of arsenical jaundice on the basis of an infectious agent. In an analysis of 119 cases of early syphilis it was found that 76 per cent of the jaundice occurred during the twelfth to the seventeenth week of treatment. On the assumption that the disease is caused by an infectious agent, that it was spread not by contact but by inoculation when injections of an arsenical were being given, and that infection usually occurred at the time of the first few injections, the authors suggest that the incubation period is from twelve to seventeen weeks. It is further suggested that postarsphenamine jaundice may be identical with the jaundice which occurs after the administration of human blood products or of yellow fever vaccine containing human serum and that imperfectly sterilized syringes permit such inoculation. An experiment is cited whereby each of 10 patients with early syphilis was given a new unused syringe for his exclusive use for all injections. Sterilization was accomplished by boiling the syringe before and after each treatment. Only 4 of the 10 were observed beyond one hundred and twenty days after the first treatment. Jaundice did not appear in any of this group, but 1 of them later received two injections of an arsenical at another clinic from syringes used on other patients. These syringes were sterilized not by boiling but by rinsing in 70 per cent alcohol. Eighty-three days thereafter the patient became jaundiced. The authors state, "This series, though short . . ., is strongly suggestive of blood transmission."

There has been much speculation as to whether this enormous incidence of jaundice may be due to dietary deficiencies. There are two outstanding lacks in British wartime diet: ascorbic acid (citrus fruits) and meat proteins. It has been repeatedly shown, in Great Britain and elsewhere, that ascorbic acid neither protects against nor shortens the course of arsenical jaundice. Experimental studies are now under way concerning the effect of protein, especially amino acid, treatment of that condition.

According to Kopp and Solomon,[75] tryparsamide causes little damage to the hepatic parenchyma, even when administered over a prolonged period of time and combined with fever therapy. A survey of the use of this drug in the Boston Psychopathic Hospital, with administration of 43,000 injections to 829 patients, revealed no deaths nor any instances of acute yellow atrophy. Jaundice occurred in 3.6 per cent of the patients treated, but this was benign and of brief duration and in most cases it was possible to resume the use of the drug within a few months after the jaundice had cleared.

Studies of hepatic function (sulfobromophthalein sodium retention tests; determinations of phospholipid, hippuric acid excretion, fibrinogen and cholesterol; cephalin-cholesterol flocculation tests; determination of total bilirubin; van den Bergh test reaction, and determination of icterus index) were made on 66 patients with syphilis of the central nervous system to whom repeated injections of tryparsamide had been given. Of the 66 patients, 51 had also received some form of fever therapy. There was slight evidence of impaired hepatic function in 34 patients. Although therapeutic fever produces impairment of hepatic function the administration of tryparsamide following fever did not aggravate this condition. The subsequent administration of large amounts of tryparsamide to patients in whom hepatic dysfunction had developed after the use of trivalent or pentavalent arsenicals did not cause a recurrence of the jaundice, nor was the function of the liver significantly impaired.

*Acute Nephrosis.*—Thomas and his co-workers [76] have administered combined arsenical and

73. Maclagan, N. F.: The Serum Colloidal Gold Reaction as a Liver Function Test, Brit. J. Exper. Path. **25**:15 (Feb.) 1944.

74. Beattie, J., and Marshall, J.: Aetiology of Postarsphenamine Jaundice, Brit. M. J. **1**:547 (April 22) 1944.

75. Kopp, I., and Solomon, H. C.: The Effect of Prolonged Tryparsamide Therapy upon Liver Function, Am. J. Syph., Gonor. & Ven. Dis. **27**:445 (July) 1943.

76. Thomas, E. W.; Wexler, G.; Schur, M., and Goldring, W.: Acute Nephrosis Complicating Two Day Arsenic and Fever Therapy for Early Syphilis, J. A. M. A. **122**:807 (July 17) 1943.

fever therapy to 48 patients. Their schedule of treatment consisted of two intravenous injections of mapharsen, of 100 and 60 mg. respectively, on the first day, followed on the second day with two injections of 60 mg. each and artificially (cabinet) induced fever to a temperature of about 105.8 F. for several hours.

In 4 of the 48 patients acute nephrosis developed. An additional 4 patients had severe albuminuria and azotemia of short duration. That the azotemia was due to intrinsic renal damage rather than to hemoconcentration is evident because of the absence of dehydration and the prompt loss of renal concentrating capacity. All patients recovered from the acute episode.

*Drug Sensitization.*—After a comprehensive discussion of serum sickness, Longcope [77] is interested to compare certain types of drug reactions with the clinical picture of classic serum disease. Three groups of drugs produce a variety of sickness, simulating in many respects serum sickness: these are nirvanol (the sodium salt of phenylethylhydantoin), the arsphenamines, and the sulfonamide compounds. Nirvanol, a drug used some time ago in the treatment of Sydenham's chorea, produces the same symptoms and signs with great regularity in all patients, with much the same incubation period. Erythema of the ninth day, a febrile exanthem appearing approximately nine days after the first injection of one of the arsphenamines, is an extremely interesting illness. Among the numerous intoxications resulting from arsenotherapy, it resembles serum sickness more closely than any other. In general, the reactions to sulfonamide compounds fall into three categories: (1) acute hemorrhagic anemia; (2) agranulocytosis, and (3) febrile constitutional reactions accompanied in most instances by cutaneous eruptions.

These three groups of drugs produce systemic reactions analogous to serum sickness in its normal, accelerated and immediate form; but these reactions differ from serum disease in that specific antibodies have not so far been demonstrated in the serum and that cutaneous reactions to the specific drugs are rarely obtained.

*Arsenical Reactions in the Navy.*—The most recent compilation of data from the United States Navy concerning reactions to arsenicals is presented by Carter, Chambers and Anderson.[78] For the past eighteen years, medical officers of the Navy have been required to submit reports of the number of doses of arsenicals and the reactions therefrom. During this period, 1,914,519 doses were administered with 53 fatal reactions, a ratio of 1 death to 36,123 doses. Of the 53 deaths, 50 were due to neoarsphenamine and 1 each to arsphenamine, silver arsphenamine and mapharsen. A total of 397,680 doses of mapharsen have been administered.

*Tryparsamide Amblyopia.*—Potter [79] discusses the chemical nature of the drug, the effect of syphilitic primary atrophy of the optic nerve on visual reactions, the characteristics of the visual fields, the effects of tryparsamide therapy when syphilitic primary atrophy is present, subjective ocular symptoms during tryparsamide therapy, objective impairment of vision, alteration of light sense during tryparsamide therapy, acute visual reactions to tryparsamide, the mechanism of damage to the nerve and retina cause by tryparsamide and, finally, the medicolegal aspects of tryparsamide therapy. He says:

> ....In the introduction to this review the factors operating to veil the entire subject in factual obscurity were elucidated. Such analytic data as may be reasonably derived are approximately as follows:
>
> There is noted no indication that sex, race or age of the patient is related to untoward visual effect during therapy with tryparsamide . . . It has been noted that reports pertinent to the visual effects of tryparsamide therapy appearing in the foreign literature have shown both a higher and a lower incidence of unfavorable visual involvement than has been noted in the recent domestic literature. The fact that tryparsamide was first available in this country would suggest that the recent discrepancies of the foreign literature are comparable to the confusion indicated in American literature during the first years after the clinical introduction of the drug into this country. . . .
>
> The dose of the individual injection, the number of injections and the length and number of courses of injections have not been noted to be associated with visual effects in a consistent manner.... The number of doses of tryparsamide has long been a factor acknowledged to be associated with visual deterioration. It is generally considered that if untoward effects are to occur, these will be noted prior to the tenth injection. Evidence of such a belief is current throughout the literature. Statistically, however, such a presupposition is apparently poorly borne out, and in the light of the figures presented, which are the most complete available on this particular phase of the subject, the opinion is best modified to state that most reactions, especially "acute" ones, are noted relatively early in the series of tryparsamide injections, but such a statement must not preclude recognition that deleterious effects may occur later in the period of treatment....
>
> ....Types of visual effects are designated....as acute and chronic, with the latter type subdivided into objective and subjective. The chronic subjective reaction is characterized as occurring in approximately 5 to 10 per cent of patients receiving tryparsamide therapy and

77. Longcope, W. T.: Serum Sickness and Analogous Reactions from Certain Drugs Particularly the Sulfonamides, Medicine **22**:251 (Sept.) 1943.

78. Carter, T. J.; Chambers, W. M., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1942 with Special Reference to Arsenical Dermatitis, U. S. Nav. M. Bull. **41**:1777 (Nov.) 1943.

79. Potter, W. B.: Visual Impairment During Tryparsamide Therapy, Arch. Ophth. **30**:669 (Nov.) 1943.

consists of flashes, sparks or spots before the eyes, together with visual distortions and slightly decreased central visual acuity. Objective findings are not usually detected; the prognosis is good if therapy is discontinued....

Objective chronic reactions are specified to occur in a smaller number of patients (4 to 5 per cent) receiving tryparsamide therapy, with permanent unfavorable results in about 1 per cent. This type of reaction consists of contraction of the visual field, involving primarily the upper and lower nasal areas, with relative sparing of the temporal portions. Moderate depression of central vision is frequently noted; central scotomas and enlargement of the blindspot are not characteristic of this type of reaction. The prognosis regarding restoration of vision is held to be good if the condition is recognized and the drug withdrawn promptly. There is sufficient evidence that after an initial visual reaction the deleterious effect will recur on resumption of tryparsamide therapy to render it advisable to withdraw the drug permanently once an untoward effect of either an objective or a subjective character is noted....

Acute reactions are distinct from chronic reactions in all characteristics, including, possibly, even causation. The percentage incidence of such reactions to tryparsamide therapy is not disclosed in a review of the literature; certainly, however, they are much more infrequent than chronic ones. Usually occurring prior to the fifth injection of the drug, they are characterized by rapid deterioration of both central and peripheral vision. Complete details in a sufficient number of cases are not available in the literature to indicate in a satisfactory manner the actual outcome of the original visual deterioration. Such cases as are deemed eligible in a statistical consideration of the prognosis of such reactions indicate that in approximately one half permanent visual loss will obtain, while in the other half relatively complete restoration of vision may occur.

The foremost question with regard to the use of tryparsamide has revolved around the question of atrophy of the optic nerve and the suspected effect of the drug when this condition is noted prior to the initiation of tryparsamide therapy. It is permissible to state that opinion in regard to this matter as reflected in the literature is approximately equally divided among physicians who when primary syphilitic optic nerve atrophy is present would withhold the drug and those who under similar conditions would favor its use. Any preponderance of opinion evaluated in terms of the evidence presented would incline to the view that detectable syphilitic involvement of the visual tracts offers some type of predisposition or possibly sensitization to the drug, but there is lacking indication that the presence of optic nerve atrophy actually establishes a satisfactory contraindication to use of the drug....

That the differential diagnosis between the normal condition of the optic disk and that of primary syphilitic optic nerve atrophy is not always clearcut is attested by the fact that the color of the disk, the visual acuity and the visual field findings may yield contradictory evidence. With the introduction of the numerous complex factors associated with visual impairment during treatment with tryparsamide, confusion as to the probable cause of visual impairment is present. Of the various examinations available, apparently the examination of the visual fields offers the most thorough information in regard to the exact nature of impairment of vision....

The intimate or exact nature of the reaction to tryparsamide remains obscure in the literature. Repeatedly suggested to explain visual involvement are a hypothetic toxic effect of the drug on the nerve or retina, idiosyncrasy to the drug, factors superimposed by drug therapy on active syphilitic involvement (reactivation of a process) and the Jarisch-Herxheimer reaction. Factors such as the valence of the arsenic in the preparation, the structure of the tryparsamide molecule and the factors of retention-excretion and metabolism have been considered without the establishment of a conclusive opinion concerning the mechanisms of the reaction.

The relatively infrequent occurrence of systemic effects is against any theory holding tryparsamide to be a toxic drug generally; contrarily, the type of visual impairment is suggestive of a toxic effect in the nature of an idiosyncrasy, especially in the acute reactions. There is an absence of proof that syphilis or any other condition predisposes to a reaction to tryparsamide. There is, however, the implication that the exact mechanism of the acute and of the chronic type of reaction may be different. In the light of the clinical and pathologic material available in the literature other factors functioning to produce visual involvement cannot be adequately evaluated....

Visual reactions occurring during tryparsamide therapy have been classified as acute and chronic. Comparatively little attention has been given to the acute type of reaction. Potter[80] reports 4 cases of this type. In each of these a sudden and rapid loss of vision was experienced after from one to three doses of tryparsamide, representing the only acute reactions which occurred in approximately 500 patients treated with this drug. On this basis, the incidence of the acute type of visual reaction is less than 1 per cent. Other reports suggest a higher incidence rate. There were 3 females and 1 male, in none of whom did a complete history or physical examination reveal the presence of any disease other than tabes or tabetic dementia paralytica. In each instance a standard dose of 3 Gm. of tryparsamide was administered intravenously. The reaction was uniformly characterized by progressive loss of vision beginning approximately twenty-four hours after the injection. In 2 of the patients contraction of the visual fields to within 5 degrees of the fixation point was noted; in the other 2, central and peripheral vision were completely lost. Two of the patients were satisfactorily followed over a period of one year; in 1 the vision returned to normal but the other showed little improvement.

### EARLY SYPHILIS

*Intraurethral Chancre.*—The not uncommon occurrence of intraurethral chancre is again emphasized by Loveman and Morrow,[81] who observed 8 such lesions in a total of 70 penile chancres during a period of six months. In each instance the lesion was definitely endourethral.

80. Potter. W. B.: Acute Visual Impairment During Tryparsamide Therapy, South. M. J. **36**:697 (Oct.) 1943.

81. Loveman, A. B., and Morrow, R. P.: Intraurethral Chancre, Am. J. Syph., Gonor. & Ven. Dis. **28**:79 (Jan.) 1944.

In all the cases the diagnosis was confirmed by the dark field demonstration of T. pallidum in either the urethral discharge or the satellite bubo or both. The authors emphasize the common manifestations of intraurethral chancre: serous or serosanguineous urethral discharge in which gonococci cannot be demonstrated, palpable induration along the urethra and satellite adenopathy. The necessity for serologic follow-up of all patients with a urethral discharge is again stressed.

*Lymph Node Aspiration.*—The value of dark field examination of material obtained by lymph node aspiration in the diagnosis of early syphilis is reemphasized by Loveman and Morrow.[82] They report positive results of such examination in 23 of 25 cases of early syphilis. In 12 cases (60 per cent), dark field examinations of the local lesion failed to reveal the organisms, and the blood of 36 per cent of these patients gave a negative serologic reaction for syphilis. As to the possibility of the presence of nonpathogenic spirochetes in lymph nodes, 15 patients with nonsyphilitic adenopathy were examined with negative results. The technic of lymph node aspiration is simple and easily mastered and aids in early diagnosis, the latter being particularly important under conditions of military medicine.

*Histologic Picture of Lymphadenitis of Secondary Syphilis.*—Evans [83] calls attention to the striking histologic similarity existing between the lymphadenitis of secondary syphilis and so-called giant follicular lymphadenopathy.

Two illustrative cases are presented as well as photomicrographs of the lymph glands. The histologic changes noted in the superficial lymph nodes of secondary syphilis bore such striking resemblance to those of giant follicular lymphadenopathy that there appeared to be a possibility of mistaking syphilitic lymphadenitis for that disease. In the 2 illustrative cases, T. pallidum was demonstrated by a silver stain.

*Syphilitic Meningitis.*—Skogland [84] briefly discusses the clinical and laboratory findings of syphilitic meningitis. He analyzes the records of 15 patients with acute syphilitic meningitis who had been admitted to Charity Hospital of New Orleans over a ten year period. All patients in this study were young adults ranging from 17 to 43 years of age. Ten were Negro, and 5 were white. Males outnumbered females 11 to 4. Presumably all the patients had acquired syphilis, but for the majority it was impossible to determine the exact date of infection. Only 4 patients had knowledge of a chancre. The duration of infection before the onset of meningitis in these 4 varied from six months to two years. Eight patients in the entire group had received previous antisyphilitic treatment, consisting of either arsenic or bismuth or both. In all instances treatment was inadequate, and each of the patients had lapsed from treatment before the appearance of meningeal symptoms.

Four patients were classified as having acute syphilitic hydrocephalus; all had severe headache; nausea and vomiting occurred in 2. Rigidity of the neck was present in 3. The eyes of 3 were not examined, and in the other the disks were normal. Five patients were designated as having acute syphilitic meningitis of the vertex. In addition to the meningitic symptoms, these patients had mental symptoms, convulsions or focal phenomena. Four were delirious and 1 lethargic. A single patient suffered convulsions. No gross focal defects were encountered, but in 1 instance there existed unilateral hyperreflexia together with a positive Babinski sign. All of these patients complained of headache accompanied by nausea and vomiting. Subjective indications of meningeal irritation were evident only in 2. Edema of the optic disks was noted in 1 of 3 patients examined ophthalmologically. In the remaining 6 patients the meninges at the base of the brain seemed principally involved, as was indicated by the development of palsies of cranial nerves. Three had involvement of the third nerve alone; 2 had isolated palsies of the facial nerve of the peripheral type. In both instances the lesion was unilateral. Multiple cranial nerve palsies were encountered in 1 patient. In this patient the pupils were fixed and there were weakness of the right side of the face and right-sided deafness. All the patients in the group experienced headache, although only 2 complained of nausea or vomiting. The eyes of 3 patients were examined, and papilledema was observed in 2.

Only mild systemic reactions accompanied the meningitis. Five patients had no fever during their hospitalization; 6 exhibited mild elevation of temperature, to no higher than 102 F.; the remaining 4 had maximum elevations to between 103 and 104.6 F. At the time meningitis developed, 10 of the 15 patients in the series (66.7 per cent) had a positive serologic reaction of the

82. Loveman, A. B., and Morrow, R. P.: The Value of Darkfield Examination of Lymph Nodes in the Diagnosis of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:44 (Jan.) 1944.

83. Evans, N.: Lymphadenitis of Secondary Syphilis: Its Resemblance to Giant Folliculitis Lymphadenopathy, Arch. Path. **37**:175 (March) 1944.

84. Skogland, J. E.: Acute Syphilitic Meningitis: A Clinical Study of Fifteen Cases, South. M. J. **36**:809 (Dec.) 1943.

blood for syphilis. Of the remaining 5, 3 had received previous antisyphilitic therapy.

In all cases the cerebrospinal fluid was abnormal at the time of the first lumbar puncture. The pressure was increased in 5 instances, the maximum elevations being to 600 mm. of water. The white cell count varied from 10 to 600 per cubic millimeter. In 6 of the 7 cases in which differential counts were made the cells were predominantly lymphocytes. In a single instance polymorphonuclear leukocytes predominated at the time of the original examination, but after a few days the cells were preponderantly lymphocytes. The tests for globulin regularly gave positive results. The colloidal gold curve was negative in 6 cases, abnormal in 5 and undetermined in 4. The Wassermann reaction of the cerebrospinal fluid was positive in 13 cases (86.7 per cent of the entire group).

Symptoms abated promptly after institution of antisyphilitic therapy. As a rule, improvement was noted within a few days after specific treatment had been started and in a week to ten days there was symptomatic recovery. Except for pupillary abnormalities the cranial nerve palsies disappeared.

*Syphilitic Nephrosis.*—Of the infections which apparently cause the nephrotic syndrome syphilis is one of the most definite. Klein and Porter [85] believe that from a pathologic standpoint syphilis has definitely been proved to be responsible for nephrosis. They report 1 case of syphilitic nephrosis, that of a 16 year old Negro girl with secondary syphilis who had clinical and laboratory findings consistent with nephrosis. She responded dramatically to antisyphilitic therapy.

### TREATMENT OF EARLY SYPHILIS

*Intensive Arsenotherapy.*—Cole and his associates [86] present a review of the current methods of intensive therapy, including the intravenous drip of Chargin, Hyman and Leifer, modifications of this plan described by Schoch and Alexander and by Eagle and Hogan, and combined arsenotherapy and fever therapy. They say:

> It is fair to say that from the data given here evidence is presented showing that early syphilis is being cured by intensive treatment methods, whether it be intravenous drip, the syringe technic, multiple injections of Eagle, or fever therapy and intravenous drip or syringe treatment plus fever. The patients are not only cured but, as Schoch and Alexander show, they are even being reinfected in appreciable numbers.

85. Klein, A., and Porter, W. B.: Nephrosis Associated with Early Active Syphilis, South. M. J. **36**:694 (Oct.) 1943.

86. Cole, H. N.; Heisel, E. B., and Stroud, G., III: Intensive Methods of Treating Syphilis, J. A. M. A. **123**:253 (Oct. 2) 1943.

At the Cook County Hospital the five day drip treatment was instituted as a clinical experiment, and from August 1940 to January 1943 a total of 481 cases were studied (Rattner [87]). There have been no fatalities in the group, although there have been 3 instances of toxic encephalopathy. In the beginning of the study, mapharsen was the sole drug employed. However, at the end of the first year analysis of material disclosed the fact that in 12 to 15 per cent of the cases the treatment was a failure. In the hope of reducing the incidence of failures, the technic was then modified so that a bismuth compound was administered in addition to mapharsen. A soluble bismuth preparation was employed and given intramuscularly at daily intervals. Of the entire group of 481 patients, 421 completed a full course of five day treatment, 310 of these receiving mapharsen alone and 110 combinations of mapharsen and bismuth. Sixty patients did not complete the course of treatment, on the basis of being "medically unfit" or reacting unfavorably to the drug, or for nonmedical reasons.

Of the 310 patients who were treated with a single course of mapharsen over the five day period, 200 were observed for five months or longer. Eighty-six per cent were considered as showing satisfactory results; failures were encountered in 11.5 per cent; and results were still pending for 2.5 per cent.

Of the group of 111 patients treated with one course of mapharsen and bismuth used concurrently, the results for 35 could not be evaluated because of the brief period of observation. Of the remaining 76 patients, 50 came to have negative serologic reactions, 21 showed progressive serologic improvement and 1 had a serologic relapse; the outcome therefore is still questionable. Satisfactory results were obtained in 93.5 per cent of this group.

Craige and Sadusk [88] report observations on 73 patients (including 33 previously reported on) with early syphilis treated with mapharsen (1,200 mg.) by the five day intravenous drip method. The incidence of toxic reactions was comparable to that observed by other authors using this treatment with the exception that peripheral neuritis occurred in nearly 50 per cent of the patients. However, this was severe, with

87. Rattner, H.: The Treatment of Early Syphilis by the Concurrent Administration of Arsenic and Bismuth in a Period of Five Days, J. A. M. A. **122**:986 (Aug. 7) 1943.

88. Craige, B., and Sadusk, J. F.: Observations on the Massive-Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method: IV. Three Years of Trial, New England J. Med. **230**:314 (March 16) 1944.

involvement of motor neurons, in only 1. This patient also had jaundice—the only case of toxic hepatitis observed. Toxic encephalopathy did not occur, and there were no fatalities.

In regard to therapeutic efficacy, the data are incomplete, since only 38 patients had been observed for more than six months. Of these, 1 was believed to have been reinfected, 1 had an asymptomatic neurorecurrence, 1 a serologic relapse, and 7 continued to have positive serologic reactions six months after the completion of treatment.

Jones and Maitland [89] present a "new conception of early syphilis" based on the serologic behavior of 100 patients undergoing intensive therapy with single daily injections of mapharsen. Quantitative Kolmer-Wassermann tests were performed daily throughout the period of treatment. By a study of these serial titrations the authors found that patients with early syphilis could be divided into three different groups, designated as having early, middle and late primary syphilis, the latter two being further subdivided into types A and B.

Early primary syphilis group refers to seronegative primary syphilis (at no time is there a doubtful or positive serologic reaction test for syphilis). The authors define the types in this manner:

> The middle primary, type A is that in which there is an initial negative phase persisting for anything up to five days after the institution of treatment, followed by a sharp rise to the positive zone. This persisting for sometimes up to eight days, and not reaching above a titre of 17 (units) .... reverts immediately to negative before the completion of treatment, and except perhaps in some cases for a slight secondary very transitory rise, remains negative subsequently. Type B is that in which the titre is already rising at the beginning of treatment, but its subsequent behavior is exactly similar to Type A.
>
> The late primary, Type A is that in which the serum has already reached a high titre before treatment. This type remains at a consistently high level, which may be maintained for an indefinite period (up to six months) but which eventually reverts to negative. In Type B the titre rise takes place just after the initial injections and remains consistently at a high level for a period of approximately three weeks before reverting to normal.

These serologic types are illustrated graphically in the original article. Presumably, though it is not stated, this grouping is entirely serologic and clinically would apply to secondary as well as to primary syphilis.

The authors feel that the custom of prescribing a predetermined total dose of mapharsen, usually 1,200 to 1,800 mg., for all types of early syphilis is illogical. They believe that dosage should be regulated according to the aforementioned types of serologic behavior observed as treatment progresses. They state:

> We look on this recategorization as giving a new and original line of approach to the treatment of early syphilis by intensive therapy. It provides a fair and reliable index of the intensity of the individual patient's infection, thus allowing him the opportunity of a true scheme of treatment—abortive for the early primary and middle primary, and curative for the late primary. The duration of treatment (according to their schedule) would be 15, 20, or 30 days respectively, with dosages of 600 to 900 mgm., 900 to 1,200 mgm., and 1,200 to 1,800 mgm., depending on body weight.

It should be noted that these dosages were selected entirely arbitrarily.

One advantage of this system of treatment stressed by the authors is that the danger of serious toxic reactions is lessened. Of 100 patients so treated, agranulocytosis was observed in 1 patient, jaundice in 11 and toxicoderma in 4. Toxic encephalopathy developed in none. This incidence of toxic reactions is approximately comparable to that observed in the United States under any intensive scheme by which treatment is condensed to ten days or less.

In regard to therapeutic efficacy, 3 clinical relapses were observed and in 3 patients lesions developed which were interpreted as reinfections. The minimum and maximum post-treatment observation periods of these 100 patients are not stated, though the authors imply that this study has been in progress only eight months.

Studies have previously been reported on the concentration of arsenic in the blood following treatment by the five day continuous drip and by the multiple syringe method. Gruhzit and his associates [90] have made a study of the arsenic concentration in the blood following the so-called rapid drip method of Shaffer, one of the authors of this paper.

This method consists of giving 1.2 mg. of mapharsen per pound of body weight, or 2.5 mg. per kilogram, to a maximum dose of 180 mg., dissolved in 1,000 cc. of a 5 per cent dextrose solution. This amount of drug is given by the gravity method over a period of sixty to sixty-five minutes. Treatment is repeated daily for five days.

The authors summarize the results of their experiment as follows:

> The one hour rapid continuous drip method ... provided immediately after the first to the fifth dose an

89. Jones, T. R. L., and Maitland, F. G.: New Approach to Intensive Therapy of Early Syphilis (by Mapharsen, Arsenic Preparation), Brit. M. J. **2**:448 (Oct. 9) 1943.

90. Gruhzit, O. M.; Sulzberger, J. A., and Shaffer, L. W.: Concentration of Arsenic in Blood After Administration of Mapharsen by Rapid Drip Method: Clinical and Experimental Studies, Arch. Dermat. & Syph. **49**:321 (May) 1944.

average range of concentration in the blood stream of 78.6 to 106.4 micrograms of arsenic per hundred grams of blood. The level rapidly decreased as the sampling period was delayed, and in twenty-four hours it reached a low level of 6.86 micrograms after the first injection and of 16.84 micrograms after administration of the fifth daily dose.

In dogs administration of clinically equivalent doses of 2.5 mgm. of mapharsen per kilogram of body weight by the one hour rapid continuous drip and the rapid syringe methods resulted immediately after administration in concentrations of arsenic respectively of 112.4 and 375.5 micrograms per hundred grams of blood, or a ratio of 1:3.3. The rapid syringe method of administration produced a concentration of arsenic in the blood over three times higher than that produced with the one hour continuous drip method.

The arsenic content of the blood of dogs decreased rapidly with delay of sampling for one, three, six and twenty-four hours after administration of mapharsen by either the rapid syringe or the one hour continuous rapid drip method.

The concentration of arsenic in the blood of human patients and of the dogs reached about the same level one hour after administration irrespective of the method of administration.

The slow continuous drip method administration provided about 12 to 33 micrograms and the one hour rapid drip method 78.6 to 106.4 micrograms of arsenic per hundred grams of blood immediately after administration. The rapid syringe method produced levels of 24.5 to 41.5 micrograms one-half hour after injection.

After the rapid drip method of administration, mapharsen rapidly disappeared from the peripheral blood stream. The highest concentration was found immediately after administration. There was no constant level of arsenic in the blood of clinical patients or of dogs used in experimental studies.

With the one hour rapid drip administration the arsenic content of the blood varied in different patients from about 59.7 to 127.8 micrograms per hundred grams of blood immediately after completion of administration to 24 to 68 micrograms one hour after administration, 5.8 to 34.5 micrograms six hours after administration and 4 to 20 micrograms at the end of twenty-four hours after administration.

The one hour rapid continuous drip method of administration of mapharsen caused a slight rise in the arsenic level of the blood stream after administration of five successive daily doses. There was no cumulative retention of arsenic in the blood stream in this group of patients.

*Combined Fever Therapy and Mapharsen.*—In past years there have been scattered reports which suggested that in experimental animals syphilis could be cured by combining subcurative doses of arsenical with subcurative amounts of fever treatment.

Recently clinicians have been treating early syphilis with combined artificial fever and mapharsen. Since the height and duration of the fever and the amount of mapharsen necessary to "cure" early syphilis are unknown, it becomes necessary to try various arbitrary treatment schedules.

Jones and co-workers[91] report preliminary observations in the treatment of early syphilis with combined fever and chemotherapy carried out at the Duval County Hospital, Jacksonville, Fla. Three treatment schedules have been used: (*a*) 1 mg. of mapharsen per kilogram of body weight administered during the period of induction of fever; (*b*) 1 mg. of mapharsen per kilogram of body weight administered in the evening before fever therapy and a second injection, of 1.6 mg. of mapharsen per kilogram of body weight, given after the termination of the fever; (*c*) 2 mg. of mapharsen per kilogram of body weight administered at the termination of the fever. During the entire study, fever therapy consisted of five hours with a temperature of 41.1 C. (106 F.). Because of gastrointestinal reactions, which occurred in 15 to 18 per cent of the patients, the first two methods of treatment have been discontinued. Furthermore, an additional 8 per cent of the patients treated by schedule A showed evidence of medical shock. However, the last treatment schedule (*c*) seemed to be well tolerated, and its use is being continued. A total of 410 patients have been treated by one of these schedules. No severe complications (dermatitis, hepatitis, encephalopathy or renal damage) were observed. In only 4 per cent of the cases was it necessary to discontinue treatment.

As to therapeutic efficacy, data are available on 280 patients, the majority of whom have been followed for only brief periods. Of 72 patients treated according to schedule A, all followed for at least six months, 13 (18.1 per cent) had a clinical relapse, and an additional 6 patients were thought to have been reinfected. Of 122 patients treated according to schedule B and followed for four to six months only, 7 (5.7 per cent) have thus far shown clinical relapse and 1 was thought to have been reinfected. Of 86 patients treated according to schedule C, none of whom have been followed for longer than four months, 2 (2.3 per cent) have shown clinical relapse to date. In view of the low cost and short duration of treatment and of the low incidence of toxic reactions, the authors feel that this method of treatment deserves further study.

Thomas[92] reviews experimental data on the treatment of early syphilis with fever, which emphasize that, although fever will cause disappearance of spirochetes and healing of lesions, the disease is not cured but is prone to relapse

91. Jones, N.; Carpenter, C. M.; Boak, R. A.; Warren, S. L., and Hanson, H.: The One-Day Treatment of Syphilis with Fever and Mapharsen, Ven. Dis. Inform. **25**:99 (April) 1944.

92. Thomas, E. W.: Fever as an Adjuvant to Specific Therapy in Syphilis, New York State J. Med. **44**:157 (Jan. 15) 1944.

in three to six weeks. For best results following chemotherapy alone, if treatment is to be confined within a period of five to ten days, a total of at least 1 Gm. of arsenoxide must be administered either by intravenous drip or by multiple syringe injections. From available statistics the incidence of arsenical encephalopathy with this dosage is about 1 per cent, and that of death is in the neighborhood of 0.3 per cent. In the hope of lowering this incidence of serious reactions, the author combined fever with mapharsen with the idea that fever therapy would protect the patient against the more toxic reactions and that it would be possible to achieve good therapeutic results with a lower dosage of mapharsen. Actual experience with fever combined with intensive mapharsen therapy in early syphilis failed to confirm the impression that fever protects against reactions to arsenical drugs, nor could it be proved that fever has any protective effect against toxicity of mapharsen in rabbits. It was demonstrated that by combining fever with mapharsen the same therapeutic results could be achieved with about half the total amount of mapharsen that was required when fever was not used.

At the Bellevue Hospital, 1,280 patients with early syphilis were treated by various intensive methods of therapy. Over 950 of these were treated with some combination of fever and mapharsen. Fever was induced in 890 cases by intravenous injections of typhoid vaccine. Although it was realized that this was not the best available pyrogenic agent, it was the most practical means available for inducing fever when patients were also receiving mapharsen. There were no serious accidents which could be attributed to typhoid vaccine. The present plan of treatment consists of ten daily injections of about 60 mg. of mapharsen combined with induction of fever every other day. Each patient receives about 60 mg. of mapharsen and four sessions of fever in a ten day period. The highest percentage of satisfactory results after one or more years of observation occurred in a group of patients who received four fever treatments induced by typhoid vaccine and only 0.54 Gm. of mapharsen. The number of failures of treatment among patients receiving less than 0.8 Gm. of mapharsen alone was significantly higher than when fever was combined with even smaller total doses of mapharsen (22 and 14 per cent, respectively).

It is therefore felt that fever is an important aid in the therapy of early syphilis. The fact that relapses were no more common among patients who had rather poor elevations of temperature with typhoid vaccine than among those who had temperatures up to 106 F. suggests that it is not the height of temperature alone which influences the cure. This may be another argument in favor of the theory that the physiologic effect of fever in the host is more significant than the direct effect of high temperatures on the spirochete. Also, that the effect is not due to a foreign protein reaction is suggested by the fact that if mechanical fever is used in conjunction with mapharsen the results are as good or better.

Clinical improvement may follow treatment of neurosyphilis with fever alone, but if relapses are to be prevented additional chemotherapy is required. The sooner mapharsen is used after fever and the more intensively it is given, the better the results are likely to be. When fever is induced by mechanical means, mapharsen can be given with the fever and on intervening days. However, when fever is induced by malaria arsenical drugs must be withheld until the fever is stopped, because mapharsen tends to be antimalarial.

Little statistical information is available as to the effect of fever in late latent or other types of late syphilis with negatively reacting spinal fluid. There is every reason to believe, however, that it should be as effective for such infections as it is for neurosyphilis.

An editorial writer[93] states that one of the outstanding contributions of physical medicine to the therapeutic armamentarium of the medical profession is the development of artificial fever therapy.

> The fever-chemotherapy method in its present stage of development consists of a preliminary period of a few days' observation and preparation in the hospital, an eight hour fever accompanied by chemotherapy and a post-fever hospital observation period. The preliminary preparation consists of a study and adjustment of the patient's fluid and electrolyte balance, the administration of adrenal cortex if needed and such other measures as may seem indicated. On the day previous to the eight hour fever the patient is given a short preliminary tempering exposure in the fever cabinet and also an injection of 2 cc. of the suspension of bismuth subsalicylate in oil. On the day of the treatment he receives eight hours of fever at 106° F. together with 1.76 mgm. of mapharsen per kilogram of body weight. The mapharsen is given in three equal doses: one when the patient's temperature reaches the desired level, one at the beginning of the third hour and the last at the beginning of the fifth hour. Patients are dismissed from the hospital on the third day if there are no lesions of the skin or mucosae. They return at weekly intervals for clinical and serologic examination until all lesions are healed, then every two weeks until two consecutive negative serologic tests have been obtained and thereafter at monthly intervals.

93. Intensive Fever-Chemotherapy in Early Syphilis, editorial, Arch. Phys. Therapy **25**:109 (Feb.) 1944.

The intensive fever-chemotherapy accomplishes in a few hours what has previously required several weeks or months of injection treatment. Even the new intensive chemotherapy without fever requires twice the period of hospitalization needed for the intensive fever-chemotherapy. The quantity of arsenic given in the former procedure is ten times that used in the latter. Toxic reactions but no deaths occurred in about 10 per cent of the 200 patients reported as treated by intensive chemotherapy at the Intensive Treatment Center. Of the 774 patients treated by intensive fever chemotherapy two died as the result of complicating tuberculosis. However, after further modification of the method 488 patients were treated without serious mishap.

The clinical results obtained by these two intensive methods are excellent. Among 172 patients treated by intensive chemotherapy and observed for seven months, 5.8 per cent were failures. Of the 488 patients treated by modified fever-chemotherapy only 1.6 per cent were failures. The authors conceded, however, a doubt voiced by others, that it is too early yet to pass final judgment on these intensive methods of treatment in early syphilis; more relapses may yet occur with continued observation. Even though the number of relapses, however, following intensive fever-chemotherapy, may increase somewhat, it is not likely that they will reach such proportions as to render the method of little value.

Lowe [94] reviews much of the recent American literature concerning the utilization of artificial fever therapy, alone or in combination with chemotherapy, for the treatment of early syphilis and neurosyphilis.

*Treatment-Resistant Syphilis.*—Because of differences in recorded medical opinion on the value and mode of action of arsenoxide (mapharsen) in the therapy of patients with treatment-resistant syphilitic infections, Beerman, Ingraham and Pariser [95] have summarized their experience with the use of this drug for 7 such patients. Of their 7 patients with resistance to arsenical therapy, mapharsen was effective in 3 and of no value for 3. The effect on 1 could not be decided because the concurrent use of bismuth confused the interpretation of the outcome. To the authors these results indicate that arsenoxide is not the "avid" arsenical derivative, and that the compound acts in treatment-resistant syphilis in the same manner as other arsenicals substituted for an arsenical to which the infection had remained resistant. This study affords no clue as to the mode of action of arsenoxide in cases in which the drug was successful nor does it disclose why the drug was ineffectual in other cases.

Schoch and Alexander [96] discuss the relationship of treatment resistance to relapse during or after intensive arsenotherapy.

94. Lowe, F. A.: Physical Fevers and Syphilis, Arch. Phys. Therapy **24**:587 (Oct.) 1943.

95. Beerman, H.; Ingraham, N. R., Jr., and Pariser, H.: The Problem of Treatment-Resistant Syphilis: The Value of Mapharsen (Arsenoxide) in the Healing of Lesions, Am. J. Syph., Gonor. & Ven. Dis. **27**:460 (July) 1943.

## LATE SYPHILIS

*Frequency of Syphilitic Lesions at Autopsy.*—In three previously reviewed papers,[1] Rosahn and Black-Schaffer review the literature pertaining to the frequency of acquired syphilitic lesions discovered at autopsy in persons over 20 years of age, describe the statistical methods employed in making this study and in their last paper give the morbidity and mortality findings obtained from the analysis of 5,300 autopsies performed at the Yale University School of Medicine.

In a fourth paper,[97] based on the same autopsy material, they ask some of the most important questions in the field of syphilology. Among these are the following:

> What proportion of individuals with positive serologic tests as the only indication of infection can be expected to show organic lesions or to develop them in the future, and what is the probability that these changes will be primarily responsible for death? What proportion of those with a clinical history of syphilis and negative serologic tests can be expected to harbor the infection and to die therefrom? When serologic reversal has occurred, either spontaneously or following recognized specific therapy, what is the expectation that organic lesions if present will completely regress leaving no evidence of their previous existence? When serologic reversal does not take place in spite of persistent therapy, what is the probability that organic lesions will persist and cause incapacitating illness and death?

Unfortunately, these questions remain quantitatively without answer. Rosahn has clearly shown that anatomic lesions of late syphilis can exist without accompanying positive serologic reactions of the blood and, conversely, that positive reactions of the blood may persist during life in the absence of anatomic evidence of syphilitic infection. The frequency of such situations or the probability of their occurrence could not be determined from the material studied.

In the fifth paper of the series, the last so far published, Rosahn and Black-Schaffer [98] provide the final word on the much debated Warthin lesion. They call attention to the great discrepancy between the frequency of morphologic evidence of syphilis as reported by various pathologists. The highest rates were reported by inves-

96. Schoch, A. G., and Alexander, L. J.: Infectious and Serologic Relapse During Intensive Arsenotherapy of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:221 (March) 1944.

97. Rosahn, P. D., and Black-Schaffer, B.: Studies in Syphilis: I. Review of the Incidence of Syphilis in Autopsies on Adults, Arch. Int. Med. **72**:78 (July) 1943.

98. Rosahn, P. D., and Black-Schaffer, B.: Studies in Syphilis: V. An Evaluation of Fibrosis and Round Cell Infiltration of the Parenchymatous Organs (Warthin) in the Tissue Diagnosis of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:142 (March) 1944.

tigators who followed the criteria defined by Warthin, while the reports of the lowest incidences antedated Warthin's publications or the authors did not adopt his teachings.

A complete description of the so-called Warthin lesion is given and is quoted directly from Warthin's work. The authors' summary of this study is as follows:

1. Microscopic preparations of the heart, liver, pancreas, adrenals and testes from 283 syphilitic and 722 nonsyphilitic white persons were studied in order to evaluate the histologic changes of fibrosis and cellular infiltration which Warthin ascribed to syphilitic infection.

2. No qualitative difference could be discerned between the fibroid and cellular changes observed in the organs of syphilitic persons and those of nonsyphilitic controls.

3. The two groups did not differ significantly when they were compared with respect to the incidence of Warthin lesions in the heart, liver, adrenals and testes. Pancreatic lesions were probably significantly more frequent among syphilitic than among nonsyphilitic persons, but no explanation could be found for the relatively high frequency of these changes in the latter group.

4. The group of syphilitic persons was divided into two categories, those with and those without frank anatomic alterations characteristic of syphilitic infection, and the incidence of Warthin lesions of the five parenchymatous organs in the two subgroups was compared. In no instance was a significant difference found.

5. Analysis of the age distribution of persons with and without Warthin changes in the parenchymatous organs indicated that the aging process is related to the presence of these lesions.

6. The evidence does not support the concept that the microscopic tissue changes described by Warthin are pathognomonic of syphilitic infection.

*Latent Syphilis.*—Long term (over five years) follow-up of patients with latent syphilis seen at the Johns Hopkins syphilis clinic between 1914 and 1934 [99] indicates that after treatment once clinical latency has been established there is very little progression. Of 926 patients with such latent syphilis receiving no to considerable treatment, only 6.2 per cent showed any type of progression when examined five to twenty plus years after the original diagnosis (40 per cent examined after ten years). There were no more progressions among the patients receiving fifteen to nineteen injections each of an arsenical compound and a heavy metal than among those receiving much more than this amount. Cognizance was taken of the fact that patients lost from observation cannot be accurately accounted for in retrospective studies of this kind unless they are considered by some type of modified life table method.

99. Diseker, T. H.; Clark, G., and Moore, J. E.: Long Term Results in the Treatment of Latent Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:1 (Jan.) 1944.

Kaplan and Brightman [100] report on the serologic reaction of the blood following intensive treatment of early and late latent syphilis. They summarize their study as follows:

1. Among 23 patients with early latent syphilis treated with intensive intravenous mapharsen drip therapy, with or without adjunct fever therapy, 17 (74 per cent) subsequently showed a fall in serologic titer to 50 per cent of the pretreatment level, 11 becoming seronegative.

2. Among 133 similarly treated patients with late latent syphilis, 41 (31 per cent) showed a fall in titer to 50 per cent of the pre-treatment level and only 4 became seronegative.

3. The initial titer of the serologic test and the amount of mapharsen administered did not seem to influence the results. Likewise the findings among those patients in whom fever therapy was used as an adjunct did not differ materially from the findings among those treated by drip alone."

*Syphilis of the Liver.*—An outstanding contribution to the knowledge of visceral syphilis is that of Hahn,[101] who has made a comprehensive review of the literature and of the clinical material of the Johns Hopkins Hospital on the subject of syphilis of the liver. Portal cirrhosis occurring in syphilitic patients is separately considered. The following conclusions are drawn:

1. The nature of the few available observations lends credence to the theory that an actual diffuse syphilitic hepatitis is the basis of the jaundice seen in association with untreated secondary syphilis. The criteria for diagnosis include the coexistence of jaundice with infectious lesions, a benign course and a rapid response to antisyphilitic treatment. . . .

2. No support is afforded the concept that early postarsphenamine jaundice is a Herxheimer effect, or that delayed postarsphenamine jaundice is an hepatic monorecidive. The criteria for diagnosis of a true hepatorecurrence include the appearance of jaundice in association with mucocutaneous relapse, and its prompt disappearance upon resumption of antisyphilitic treatment. . . .

3. Acute yellow atrophy of the liver in association with untreated early syphilis was not observed either clinically or at autopsy. The almost complete absence of authenticated cases in the modern literature, the nonspecificity of the pathologic changes, the consistent failure to demonstrate the causative organism, and the definite relationship to arsenical therapy cast doubt upon the existence of such an entity as icterus syphiliticus gravis.

4. The gross incidence of late syphilis of the liver was 0.45 per cent. The incidence at autopsy among 1,165 adult syphilitics was 4.9 per cent. A study of the prevalence by race, sex, and age failed to reveal any significant differences.

100. Kaplan, B. I., and Brightman, I. J.: Studies on Therapeutic Procedures in Latent and Late Syphilis: II. The Quantitative Serologic Titers Following Intensive Mapharsen Drip Therapy in Latent Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:192 (March) 1944.

101. Hahn, R. D.: Syphilis of the Liver, Am. J. Syph., Gonor. & Ven. Dis. **27**:529 (Sept.) 1943.

5. An analysis of the anatomic findings in sixty-six autopsied cases of late hepatic syphilis failed to reveal a specific syphilitic diffuse interstitial hepatitis. The most outstanding characteristic was the focal gummatous nature of the process. Large irregular surface scars which descended into the parenchyma, branching out in a stellate manner, were the most frequent anatomic findings. The origin of these scars was in the healing of gummas which were located almost exclusively within them. With this healing, there occurred contraction with distortion of liver tissue resulting ultimately, if the process was sufficiently extensive, in the typical hepar lobatum. . . .

6. An analysis of the clinical findings in seventy-three cases of late syphilis of the liver verified by autopsy or laparotomy, revealed that no single manifestation was constantly or even usually present. Abdominal pain, occurring in twelve patients, was the most significant subjective complaint. Its sole distinguishing characteristic was prompt response to antisyphiltic treatment. Other even more infrequent complaints were a history of weight loss, abdominal swelling, severe gastrointestinal symptoms, febrile episodes, jaundice or bleeding. The most frequent physical finding was a palpable liver, noted in twenty-three patients. Enlargement to more than three centimeters below the costal margin, coarse nodularity, tenderness, and predominantly unilobar enlargement were respectively present ten, nine, seven and five times only. In ten patients, the spleen was palpable. Jaundice and ascites, in the absence of contributory factors, were noted in only nine and eight patients respectively. Gross gastrointestinal hemorrhage occurred only twice. Significant temperature elevation, usually not marked, was present twelve times. Sixty-six per cent of the seventy-three patients presented other evidences of syphilis on physical examination. A serologic test for syphilis was positive in 81 per cent of the sixty-three patients. Both anemia and leucocytosis were rare.

7. No patient with late syphilis of the liver had received adequate therapy for early syphilis. . . .

8. It is possible to estimate that in only six of every 1000 syphilitics is late hepatic syphilis a contributory cause of death. Additional evidences of the benign nature of the disease were the absence of significant clinical manifestations in 70 per cent of the seventy-three patients, and the prolonged course of the disease in the remaining 30 per cent. The correct diagnosis had been suggested in only 12.3 per cent of the total, and 19 per cent of the latter group. Portal cirrhosis and carcinoma of the liver together accounted for over 50 per cent of the erroneous diagnoses recorded for those patients in whom clinical evidence of hepatic disease had been present.

9. Erroneous diagnosis was evidenced not only by failure to recognize the presence of hepatic syphilis, but also by the diagnosis of other conditions as hepatic syphilis. In only nine of thirty-five patients with an original diagnosis of syphilis of the liver, who came ultimately to autopsy or laparotomy, did the clinical diagnosis prove to be correct. Over 40 per cent proved to have portal cirrhosis, and almost 20 per cent proved to have carcinoma of the liver.

10. The diagnosis of other conditions as hepatic syphilis may be expected to become less frequent with the realization that late syphilis of the liver rarely produces arresting symptoms, with abandonment of the nebulous concept of syphilitic cirrhosis and of the fallacious use of a palpable liver as the sole criterion for diagnosis, and with the proper interpretation of the therapeutic test. In particular, hepatic syphilis rarely produces either ascites, huge livers, pronounced evidence of weight loss, high septic fever, or severe toxemia. If, however, in association with a large coarsely nodular liver, the spleen is palpable, the diagnosis of syphilis of the liver is more tenable. The therapeutic test may be adjudged to be definitely positive only if there is striking change in objective manifestations in direct temporal relationship to antisyphilitic treatment, and if such change is maintained over a long observation period. . . .

11. There was no evidence that hepatic damage due to syphilis predisposed to hepatic damage due to arsenicals. The therapeutic paradox was not observed. Nevertheless, because of the possible presence of lesions at the hilum, treatment should be initiated with bismuth and iodides. In the presence of ascites, arsenotherapy would appear to be contraindicated.

12. Portal cirrhosis occurred at autopsy in 3.8 per cent of 1,165 adult syphilitics and in 2.3 per cent of 4,505 adult nonsyphilitics. Significant differences in incidence disappeared upon elimination of those cases of cirrhosis which occurred in adequately treated syphilitics. Other cogent reasons against the assumption of an etiologic relationship between syphilis and portal cirrhosis occurred in association with definite hepatic syphilis and the absence of transition forms between the two types of pathologic processes, as well as the identity of portal cirrhosis in syphilitic and nonsyphilitic patients with respect to pathologic anatomy, incidence by race and sex, and temporal distribution of cases by four-year periods.

*Syphilis of the Bones.*—A study of 67 cases of late acquired syphilis in which changes in the bones were noted roentgenologically is reported by Francis and Kampmeier.[102] The study does not include osseous disease in congenital or early acquired syphilis. Cases with involvement of the nasal and palatine bones as well as arthropathies have been omitted from the report. In the 67 patients studied, 117 bones were found to have roentgenographic evidence of disease. Many persons had multiple osseous lesions. Since the entire skeletal system was not examined in all instances, it is probable that multiple lesions are even more frequent than are indicated by these figures.

The tibia was most frequently involved, and often there was a bilateral tibial lesion or involvement of the fibula in the same extremity. The distribution of osseous syphilitic lesions of these 67 patients is presented in tabular form. The numbers of times the various bones were involved was: tibia, 34 times; clavicle 17; skull, 15; fibula, 15; femur, 8; humerus, 5; rib, 4; ulna, 3, and scapula, 3, and other bones, to make up the series of 117, once or twice each.

The pathologic changes of late acquired syphilis of bone are generally described as periosteal

102. Francis, H. C., and Kampmeier, R. H.: The Bone Lesions in Acquired Tertiary Syphilis, South. M. J. **36**:556 (Aug.) 1943.

gumma with secondary changes and as gummatous osteitis or osteomyelitis with reaction in the surrounding bone. The necrosis caused by the gumma itself appears as a destructive or translucent area on the roentgenogram. The changes in the bones surrounding the gumma may vary in extent, shape and density. For this reason syphilitic disease of bone may simulate most other diseases which affect bone.

For simplicity in interpretation of the roentgenograms, the authors classify syphilitic lesions of bones into three groups:

(1) Periostitis, which may appear as periosteal thickening with a localized increase in density similar to cortical bone, as laminated layers, or as a diffuse, wavy cortical thickening. In periostitis, the destruction due to gumma may or may not be seen.

(2) Gummatous osteitis, destructive osteitis or osteomyelitis, which is usually associated with periosteal or endosteal changes and variable degrees of sclerosis in the surrounding bone.

(3) Sclerosing osteitis in which the gumma may be very small or obscured, and in which periosteal change is usually also present. The bone shows increased density.

An analysis of the predominating lesions in the present study showed gumma in 72 bones, periostitis in 27 and sclerosing osteitis in 16.

Because of the great variation in the osseous lesions of late syphilis, it is not always easy to make the diagnosis from the roentgenogram. Osseous lesions which are most often confused with syphilis are pyogenic osteomyelitis, tuberculosis, fungous infections, especially the mycoses, primary sarcoma and metastatic cancer. The multiplicity of lesions in syphilis and the frequency of sclerosis or osteoblastic changes are helpful differential signs. Finally the clinical history, results of physical examinations and serologic reactions of the blood must be carefully considered along with the roentgenologic findings in establishing the correct diagnosis.

*Subcutaneous Juxta-Articular Nodules.*—In a review of the subject of juxta-articular nodules, McCarthy [103] points out that, although these are commonly associated with syphilis, yaws and the arthritides, they may occur in a variety of conditions, including two important tropical diseases, filariasis and nocardiosis (a fungous infection). The latter causes should be suspected when the nodules are seen in persons returning from areas known to be infested. In filariasis, a filaria can often be demonstrated by aspiration from juxta-articular nodules, while in nocardiosis the parasite may be demonstrated in the lesion by histologic study. In other types of nodules the author reemphasizes that histologic study may be of little or no assistance in arriving at an etiologic diagnosis.

*Fever Due to Syphilis.*—Goldman and his associates [104] point out that in previous centuries fever was prominently associated with syphilitic infection. Even in the last century, articles were published describing fever in association with various types of syphilis. The present study points out that fever does not commonly accompany syphilis. The authors' conclusions are as follows:

To determine the incidence and intensity of true syphilitic fever in present-day syphilis, 2,519 unselected hospital patients representing all phases of syphilis were studied at the Cincinnati General Hospital from 1937 through 1942. Of 33 cases of chancre, only three had fever which could have been due to syphilis. Of 129 cases of secondary syphilis, in only 14 (11 per cent) was fever believed to be caused by the syphilis alone. Of 1,819 cases of latent syphilis, only one (0.05 per cent) may have satisfied the diagnosis of syphilitic fever. In the series of late cases, 464, here too the incidence of syphilitic fever was low. In practically all the cardiovascular patients with fever, this was due to "fever of congestive failure" or to local pressure phenomena plus infection. Save for the meningitides, the fever in neurosyphilis, in all save a few instances, could be due to nonsyphilitic complications. Only two patients of a series of thirteen (15 per cent) with hepatic syphilis had fever due to this cause. The series of congenital syphilis was small for critical analysis, 74 patients, but here too, and even in early active congenital syphilis, the fever could have been caused by nonsyphilitic conditions. Syphilitic fever when present in our cases was usually low grade in intensity and had no special type of curve configuration. From a critical survey of fever in present-day syphilis, the incidence is found to be much lower than that reported in older literature. This change in incidence, and perhaps intensity, may be assumed to be an additional, although minor, clinical proof of the changing character of present-day syphilis to a more benign type of infection.

### CARDIOVASCULAR SYPHILIS

*Uncomplicated Syphilitic Aortitis.*—There is still difference of opinion as to the possibility of clinical diagnosis of early uncomplicated syphilitic aortitis. Further data are presented by Mattman and Moore.[105] In 1932, Moore, Danglade and Reisinger [106] pointed out that of 105 patients found at necropsy to have syphilitic aortitis un-

103. McCarthy, C. I.: Subcutaneous Juxta-Articular Nodules: A Study of Their Clinical and Histologic Characteristics, U. S. Nav. M. Bull. **41**:1683 (Nov.) 1943.

104. Goldman, L.; Ringelman, N. P., and Claassen, H. L.: Syphilitic Fever in Present-Day Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:200 (March) 1944.

105. Mattman, P. E., and Moore, J. E.: The Clinical Diagnosis of Uncomplicated Syphilitic Aortitis, Am. J. Syph., Gonor. & Ven. Dis. **27**:711 (Nov.) 1943.

106. Moore, J. E.; Danglade, J. H., and Reisinger, J. E.: Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm: Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients, Arch. Int. Med. **49**:753 (May) 1932.

complicated by aortic regurgitation or aneurysm, the clinical diagnosis had been correctly made or suspected before death for only 17 (16 per cent). It was further suggested, however, that with due attention by clinicians to the presence of recorded symptoms or physical signs the condition might have been recognized during life in a total of 62 per cent. The present article presents an analysis of the cases of 79 additional patients observed between 1932 and 1941 who were found at necropsy to have uncomplicated syphilitic aortitis.

The criteria for the clinical recognition of uncomplicated syphilitic aortitis with modifications based on further experience are summarized by the authors as follows:

In a patient with known late syphilis (i. e., of more than four years' duration) and in the absence of hypertension, extensive arteriosclerosis or rheumatic (mitral) heart disease, the symptoms and signs of uncomplicated syphilitic aortitis include:

1. Roentgenologic demonstration of dilation of the first portion of the aorta. This should be by fluoroscopy, the use of the oblique positions, or roentgenkymography. It cannot rest on the routine posteroanterior teleroentgenogram and the Vaquez-Bordet measurements of "aortic width" unless distortion be extreme.
2. Heart failure or lowered cardiac reserve in the absence of hypertension or valvular disease. Failure may be either congestive or anginal; paroxysmal dyspnea is probably an anginal equivalent; and lowered cardiac reserve usually first reveals itself by dyspnea on exertion.
3. Localized substernal pain (to be differentiated from anginal pain), which characteristically is dull, aching, relatively constant, and is neither influenced by exertion nor referred down the arms.
4. Characteristic changes in the second aortic sound. Accentuation in contrast to the other heart sounds is the rule; and especially an alteration in quality, best described as tympanitic, bell-like, tambour, i. e., approaching a pure musical note.

On the basis of these criteria the authors record an increase in the ratio of actually correct to potentially possible clinical diagnoses from 41 per cent during the period 1910 to 1930, to 68.1 per cent in the decade 1932 to 1941. They agree that uncomplicated syphilitic aortitis is often an asymptomatic disease, but think that the extent to which this is true varies with two factors: (*a*) the extent of pathologic damage to the aorta and (*b*) the care devoted to history taking and physical and laboratory examination of the patient. The authors are convinced that the clinical diagnosis of uncomplicated syphilitic aortitis not only is possible but can be made in a substantial proportion of such cases.

Dressler and Silverman [107] present a statistical study of syphilitic aortitis and draw some remarkable conclusions. They examined 1,270 patients with proved syphilis seen over a period of two years. The features of the study were (1) to include only patients with proved syphilis, (2) to examine a large series of patients, (3) to have a single examiner see each patient, and (4) to corroborate the clinical diagnosis by instrumental methods, by follow-up study to discover complication and by postmortem examination. All of these were achieved except postmortem examinations.

Roentgenographic and fluoroscopic examinations were not done unless there was a definite clinical diagnosis of uncomplicated syphilitic aortitis, some other type of syphilitic heart disease or hypertension, or of other disease of the heart.

Of the 1,270 patients with syphilis examined, 390 (30.7 per cent) constituted the entire group of patients with cardiovascular syphilis, of whom 304 (24 per cent) were given a clinical diagnosis of uncomplicated syphilitic aortitis. One hundred and eighty-five (47.4 per cent) of the 390 patients with cardiovascular syphilis had hypertension. Of the 304 patients with uncomplicated syphilitic aortitis, 134 (44 per cent) had elevated blood pressure.

An analysis was made of the cases of the other 880 patients including the complete study to determine the incidence of hypertension. Some of these patients were without cardiac disease; some had arteriosclerotic, hypertensive, rheumatic or congenital heart disease. Of this group, 100 (11.3 per cent) had hypertension. The importance of this observation is impaired by absence of data as to the average age of the group and as to the comparative incidence of early and late syphilis.

The authors discuss the subjective and objective symptoms and signs purporting to be associated with uncomplicated syphilitic aortitis. They believe that the successful clinical diagnosis of this condition depends on the alertness and the ability of the clinician as well as on the extent and distribution of the pathologic process. It is emphasized that a clinical diagnosis of uncomplicated aortitis can and should be made in the presence of a normal-sized aorta if definite and unmistakable physical signs are present.

The presence of a large number of hypertensive persons among their patients with cardiovascular syphilis is somewhat confusing. From the statistical standpoint it was impossible to prove that this was not merely a coincidental finding. However, the authors consider that the diagnosis of syphilitic aortitis may be readily made in the

107. Dressler, M., and Silverman, M.: Cardiovascular Syphilis: An Approach to Early Clinical Recognition and Early Treatment, Ann. Int. Med. **19**: 224 (Aug.) 1943.

presence of hypertension. They also believe that uncomplicated syphilitic aortitis is not an infrequent finding in congenital syphilis.

*Functional Aortic Insufficiency.*—So-called functional aortic insufficiency without changes in the structure of the aortic valve leaflets has come to attention from time to time. This type of aortic insufficiency is usually attributed to arteriosclerosis, hypertension or chronic nephritis.

Gouley and Sickel [108] describe 11 cases of aortic insufficiency which are not easily classified because of certain clinical peculiarities. All the patients were elderly people who had repeatedly had negative reactions to serologic tests of the blood for syphilis and who at autopsy showed changes in the aortic valve different from those produced by syphilis, rheumatic fever or arteriosclerosis. The authors state:

> This lesion is a sclerotic thickening confined to the mid-portion of the free edge of the aortic leaflets. It is essentially a loss and a fibrous replacement of the original corpora arantii, without involvement of the lateral portions of the free margin of the leaflet or of the body of the leaflet, except insofar as marked central involvement necessarily extends some distance toward the periphery. . . .
>
> This lesion in the mid-portion of the free margins may assume odd shapes and attain considerable size. All three leaflets are usually involved. The central thickening may appear as a bicornate projection, with two sclerotic tips or nodules enclosing a central sector where the valvular substance has been eroded. The lesion is firm, densely sclerotic, and without resemblance either to the original corpus arantii or to verrucae. In some cases there is a rolled thickening or lipping of the free margin, most pronounced at the mid-point, and gradually tapering off into the delicate normal structure at the lateral portions of the leaflets. The bicornate and the lipped thickenings are the common types of deformity. . . . In some cases the three leaflets show different deformities; one may have central horn-like projections, the others be lipped or rolled in varying degree.

It is believed that these lesions are not responsible for aortic regurgitation but that a supravalvular dilatation which resulted in aortic insufficiency accounted for the changes seen in the valve.

*Electrocardiographic Changes in Cardiovascular Syphilis.*—A study of the electrocardiographic patterns in cardiovascular syphilis has been made by Cole and Bohning,[109] who have correlated the electrocardiograms and postmortem observations made in 30 cases. In 8 of these cases the anatomic abnormalities were entirely on a syphilitic basis; in 22 cases the syphilitic lesions were associated with other cardiovascular abnormalities. Uncomplicated syphilitic aortitis and uncomplicated aneurysm produced no electrocardiographic abnormalities. Left ventricular hypertrophy resulting from syphilitic aortic regurgitation was reflected by various types of left ventricular preponderance in the electrocardiogram. Coronary ostial stenosis produced by syphilitic lesions resulted, as a rule, in myocardial fibrosis which had no specific electrocardiographic pattern. Myocardial infarction of the anterior wall resulting from coronary osteal encroachment occurred in 3 patients, all of whom had typical electrocardiograms.

Parsonnet and Bernstein [110] find that the electrocardiographic manifestations in cardiovascular syphilis are not specific, except for a peculiar notching of the ascending limb of the QRS complex (originally described by Heimann) in a small proportion of cases. When the coronary ostia are narrowed or the myocardium itself is invaded, changes in the T wave and in the ST segment similar to those of coronary disease are often seen. The presence of changes in the ST segment and the T wave of the so-called "left ventricular strain" type is, however, due to an enlarged left ventricle and not to coronary insufficiency. Though a widened QRS complex is not diagnostically significant, this change is indicative of a grave prognosis.

*Laminagraphic Studies of the Aorta.*—Scott and Bottom [111] utilized the laminagraphic method of sectional roentgenography in the study of aortic arteriosclerosis, dissecting aneurysms and saccular aneurysms. The examination is simple, can be done by a technician and is not uncomfortable or hazardous to the patient. The unwanted shadows are dispersed to provide a uniform background. Preliminary routine roentgenograms aid in determining the positions and levels at which to make laminagrams. Laminagraphy is least applicable for children and young adults and most effective for older persons with arteriosclerosis. Sectional roentgenograms provide the most satisfactory method of demonstrating dissecting aneurysms. Saccular aneurysms can be visualized to the same advantage.

108. Gouley, B. A., and Sickel, E. M.: Aortic Regurgitation Caused by Dilatation of the Aortic Orifice and Associated with a Characteristic Valvular Lesion, Am. Heart J. **26**:24 (July) 1943.

109. Cole, S. L., and Bohning, A.: Electrocardiographic Patterns in Cardiovascular Syphilis, Am. J. M. Sc. **207**:317 (March) 1944.

110. Parsonnet, A. E., and Bernstein, A.: Significant Electrocardiographic Changes in Cardiovascular Syphilis and Their Value in Treatment, Urol. & Cutan. Rev. **47**:516 (Sept.) 1943.

111. Scott, W. G., and Bottom, D. S.: Laminagraphic Studies of the Aorta, Am. J. Roentgenol. **51**: 18 (Jan.) 1944.

NEUROSYPHILIS

*General Considerations.*—Katz and Dean [112] have subjected to critical analysis the histories of 267 patients with neurosyphilis who were observed over a period of five years. The source of patients, the diagnosis and the age distribution are presented in tabular form. They summarize the more significant findings:

1. In 122 cases, the syphilitic infection was unknown to the patient.
2. Only 9 patients received treatment for the early stage of the infection which could be termed adequate.
3. Twenty-five patients interrupted treatment of their own accord because they did not realize the seriousness of their condition.
4. Sixty-nine patients were inadequately treated or a wrong type of therapy used.
5. Examination of spinal fluid was done in only 6 instances before the onset of neurological symptoms.

*Dementia Paralytica.*—Because of the well established and adequate system of hospitals for persons with mental disease in the state of New York, reports of the Department of Mental Hygiene give an excellent picture of mental sickness in the state. From material taken from the annual reports of the department, Tietze [113] used the Reed-Merrill method of abridged life table construction to determine the chance of eventual admission to a mental disease hospital in New York state. The cumulated probability of admission for any type of mental disorder was 85.5 per thousand population born alive. The cumulated probability of admission because of dementia paralytica was 6.5 and 2.1 per thousand among males and females respectively.

*Treatment.*—(*a*) Postmalarial Chemotherapy: In the past there has been little accurate information regarding the amount of postfever treatment necessary to insure good results and prevent relapse. Ideas of expert syphilologists varied; some treated the patients until the Wassermann reaction of the cerebrospinal fluid became negative; others believed no more than six months' treatment was necessary.

Dattner and his associates,[114] realizing the dilemma, have made an excellent attempt to clarify this problem. In an earlier paper [115] they stressed the importance of examinations of the spinal fluid as the most reliable method of determining the activity of a syphilitic process in the central nervous system. It is their belief that clinical signs and symptoms alone are not reliable guides in the diagnosis and treatment of neurosyphilis. In the presence of positive Wassermann or flocculation reactions of the cerebrospinal fluid the best available guide to determining the activity of a syphilitic infection of the central nervous system is increase of cells and protein of the spinal fluid. In their previous paper, the authors summarized their conclusions as follows:

1. In untreated cases of syphilis a positive spinal fluid Wassermann reaction, with negative findings in other tests, does not prove activity. When a positive spinal fluid Wassermann test is associated with increased cells or protein, activity must be assumed.
2. In cases under specific therapy, normal cell counts and protein content in spinal fluids with positive Wassermann tests merely indicate that the infectious process is inhibited; and it may become active again within 6 months after treatment is stopped.
3. If the spinal fluid shows no more than 3 or 4 cells per cubic millimeter and definite diminution in protein content, six months after treatment has been discontinued, in all probability that activity of the syphilitic process in the central nervous system has been permanently checked, although it may require years before the complement fixation and colloidal tests become negative.

The present report, based on the criteria already outlined, sums up the experience at Bellevue Hospital in the treatment of patients with active neurosyphilis. Since Jan. 1, 1939 it has been their policy to treat all patients with "active" spinal fluids, regardless of the presence or absence of clinical signs and symptoms, with some form of fever therapy in addition to chemotherapy, unless fever was contraindicated by the general condition of the patient. Fever was induced by malaria. The number of paroxysms was limited to eight. Fever therapy was immediately followed by chemotherapy. At first the patients were given alternating courses of weekly injections of an arsenical followed by bismuth for a period of six months. In January 1940, the treatment period was shortened by giving 60 mg. of mapharsen daily for ten days following the last elevation of temperature, and at a time when the patient was still in the hospital. No further treatment was permitted. The cerebrospinal fluid was examined six months after the completion of therapy. If it contained no more than 4 cells per cubic millimeter and there was a definite reduction in protein content, the result was considered satisfactory. Patients were kept under observation and their spinal fluids examined every six months. If, however, six months

112. Katz, F., and Dean, B.: A Catamnestic Study of 267 Neurosyphilitic Patients, Canad. M. A. J. **50**:39 (Jan.) 1944.

113. Tietze, C.: A Note on the Incidence of Mental Disease in the State of New York, Am. J. Psychiat. **100**:402 (Nov.) 1943.

114. Dattner, B.; Thomas, E. W., and Wexler, G.: Rapid Treatment of Neurosyphilis with Malaria and Chemotherapy, Am. J. Syph., Gonor. & Ven. Dis. **28**: 265 (May) 1944.

115. Dattner, B., and Thomas, E. W.: The Management of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:21 (Jan.) 1942.

after fever therapy the spinal fluid showed signs of activity, the patients were either returned to the wards for retreatment or given some type of chemotherapy.

Between Jan. 1, 1939 and June 1, 1943, 419 patients with neurosyphilis were treated with malaria followed by some form of chemotherapy; 5 of those were retreated with a different strain of malaria, which made a total of 424 courses of fever treatment with malaria. Of these courses, 148 were followed by routine chemotherapy and 276 by a daily injection of 60 mg. of mapharsen for ten days. Patients were classified according to the type of neurosyphilis as follows: asymptomatic, 125; meningovascular, 35; dementia paralytica, 74; tabes dorsalis, 103; tabetic dementia paralytica, 34; tabes with atrophy of the optic nerve, 32; congenital, 16. Four of the patients with congenital neurosyphilis were children with dementia paralytica.

None of the patients who were treated with 60 mg. of mapharsen for ten days following fever therapy suffered any arsenical reactions of importance; as a matter of fact, they seemed to tolerate treatment better than those with early syphilis treated with various types of massive arsenotherapy.

Of the 419 patients (424 treatment courses), 10 died, 62 were lost from observation and 54 were treated too recently for evaluation. Consequently, the results of therapy are limited to 293 patients, or 298 treatment courses; this group has been followed from six to forty-eight months. Comparing the results of the two treatment groups, it is found that there was no significant difference between the patients who received only ten days of treatment following fever therapy and those who were given six months of chemotherapy. Therefore, the advantage of the more intensive chemotherapy lies in the fact that much time can be saved by limiting treatment following malaria therapy to ten days. There is also the advantage of completing therapy while the patient is still in the hospital, which avoids the inevitable delinquencies that occur during routine weekly injections.

(*b*) Combined Artificial Fever Therapy and Chemotherapy: It is difficult to evaluate, except in general terms, the results of Batchelor, Thomson and Huggan's [116] study of 22 patients considered to have neurosyphilis. Sixteen with dementia paralytica, 4 with tabetic dementia paralytica and 2 with symptomatic neurosyphilis, 14 of whom were incapacitated, were treated with combinations of artificial fever (inductotherm) and chemotherapy (tryparsamide, neoarsphenamine or a bismuth preparation). One half of the patients received twelve fever sessions; 3 received seven or less; only 9 had as many as thirty or more hours at 105 F. or over; 7 had less than twenty hours. Because toxic hepatitis developed in 7 of 8 patients after they were treated with tryparsamide, bismuth alone was given to the others. All the patients were treated subsequent to the fever therapy with tryparsamide or neoarsphenamine and bismuth preparation (type not stated). Observation ranged from three to thirty-four months. At the end of that period, in all except 2 cases the Wassermann reaction of the spinal fluid became negative; the colloidal gold curve was improved in all and was negative in 17, and all the patients were working. The authors make a good case for the treatment of neurosyphilis, but how much and what type they prefer is not clear.

Bennett and his co-workers [117] report clinical and laboratory data concerning 25 patients with neurosyphilis treated with artificial fever and phenarsone sulfoxylate, a relatively new pentavalent arsenical compound. Treatment consisted of fifty hours of fever with temperatures above 105 F. given in three-hour sessions every five to seven days. Bismuth subsalicylate was administered just before each treatment, and phenarsone sulfoxylate was given intravenously at the height of the fever. Follow-up chemotherapy was "routinely advised." Apparently only 12 of the 25 patients were followed more than three months. The results in the present series compare favorably with the results in a previous group of persons with neurosyphilis treated by the same authors with combined artificial fever and mapharsen therapy. The authors state that the type of arsenical used in the combined treatment does not materially affect the results.

Four of a total of 44 patients treated with combined phenarsone sulfoxylate and fever therapy had ophthalmologic complications. One patient complained of blurred vision after seven combined treatments, although objective examination was consistently negative. In a second patient, bilateral atrophy of the optic nerve developed after twelve combined treatments. In a third patient, dimness of vision developed after eight combined treatments. Examination disclosed pallor of the left optic disk. The patient's

116. Batchelor, R. C. L.; Thomson, G. M., and Huggan, J. L.: The Treatment of Neurosyphilis by Inductopyrexia and Chemotherapy, Brit. J. Ven. Dis. **19**:49 (June) 1943.

117. Bennett, A. E.; Morrison, W. H., and Modlin, H. C.: Combined Artificial Fever and Aldarsone in the Treatment of Neurosyphilis, Ven. Dis. Inform. **25**: 69 (March) 1944.

death prevented further study. A fourth patient experienced sudden loss of vision in his left eye after ten combined treatments, presumably due to retrobulbar neuritis. Later, vision "improved" (sic) so that he was able to count fingers, and the optic disk became gray.

The authors point out that previous reports of 186 patients treated with phenarsone sulfoxylate alone included only 1 patient whose ocular changes necessitated discontinuing the use of the drug. They conclude that, while phenarsone sulfoxylate may be relatively unlikely to cause untoward visual reactions when used alone, it must be used with considerable caution in combination with fever therapy.

(*c*) Fever Induced by Continuous Drip of Typhoid Vaccine: Since the original description of fever induced by intravenous continuous drip of typhoid vaccine, the method has been tried by many. All are not entirely convinced of its simplicity but many admit it has a definite place in the field of fever therapy. One of the major difficulties seems to be in the regulation of dosage of vaccine. Knight and his associates [118] have given 91 patients from one to fourteen therapeutic fever treatments, making a total of 230 individual treatments for the entire group. Fever was maintained from two to seven hours and was produced by means of intravenous drip with standard United States Army triple typhoid vaccine prepared for prophylactic inoculations.

The first treatment is usually prescribed as follows:

$$30\ \text{M} + \frac{300\ \text{M} \times 1{,}000\ \text{cc.}}{60/\text{m} \times 500\ \text{cc.}}$$

Beginning at 7 a. m.

(M = million organisms; 60/m = 60 drops per minute)

Such a prescription indicates to the nurse carrying out these treatments that at 7 a. m. the patient is to receive 30,000,000 typhoid organisms from the stock solution. At the end of one hour, the intravenous drip needle is introduced into the vein and a solution diluted to contain 300,000,000 organisms per thousand cubic centimeters of 5 per cent dextrose in isotonic solution of sodium chloride is allowed to flow in at the rate of 60 drops per minute until 500 cc. of the mixture has been given. Ordinarily at the end of two hours the temperature will have begun to rise. At this point the patient's condition determines both the dilution and the rate of flow of subsequent infusions. If the temperature is not rising as it should, the rate of flow is increased. The formula then reads: $\frac{300\ \text{M} \times 1000\ \text{cc.}}{120/\text{m} \times 500\ \text{cc.}}$, indicating that the same dilution is to be used but that the rate of flow is increased to 120 drops per minute for a total of 500 cc. If by this means the desired result is not obtained, the formula is then changed to $\frac{600\ \text{M} \times 1000\ \text{cc.}}{120/\text{m} \times 500\ \text{cc.}}$. As soon as the desired temperature is obtained, the rate of flow is decreased, usually with the concentration remaining unchanged, as for example: $\frac{600\ \text{M} \times 100\ \text{cc.}}{30/\text{m} \times 500\ \text{cc.}}$. Dosage formulas for subsequent treatments are suggested. The care of patients treated with this form of fever therapy is much the same as that with other forms of hyperthermia. The therapeutic fever levels attained in the majority of properly handled patients are comparable with fever levels attained by means of fever cabinets. By this method, therapeutic fever treatments have ranged in duration from three to ten hours and the temperature levels maintained have ranged from 104 to 106.5 F. Temperatures above 106 F. are more difficult to maintain.

The most common reactions encountered were nausea, vomiting, chills, restlessness and headache. A drop in the systolic blood pressure below 80 is a more alarming reaction, and steps should be taken immediately to restore the pressure to normal.

The advantages of this method of treatment are obvious. It does not require elaborate equipment. One nurse-technician can handle 4 patients instead of the 1 usually handled in the hypertherm. Many patients seem to like the typhoid vaccine drip better than the hypertherm. It is possible to obtain satisfactory therapeutic temperature curves with this treatment.

It is emphasized that adherence to technic and training of personnel in the proper management are of prime importance for the successful administration of this form of treatment. It is inevitable that without preliminary groundwork there will be reactions, and possibly fatalities, which will militate against popular approval of the method as a whole.

Lawrence [119] has given four hundred hours of fever with temperatures over 104 F. to 10 patients by allowing triple typhoid vaccine to drop into their veins slowly. The method adopted is that previously described by Solomon and Somkin.[1h] The author believes the method is applicable to army facilities, since all it requires is typhoid vaccine, infusion apparatus and nursing personnel. None of the 10 patients treated had any serious complications, although 2 of them

118. Knight, H. C.; Emory, M. L., and Flint, L. D.: A Method of Inducing Therapeutic Fever with Typhoid Vaccine Using the Intravenous Drip Technic, Ven. Dis. Inform. **24**:323 (Nov.) 1943.

119. Lawrence, H.: Induction of Fever by the Intravenous Infusion of Triple Typhoid Vaccine in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:289 (May) 1944.

suffered vasomotor collapse which responded rather readily to corrective measures.

*Complications of Therapeutic Hyperpyrexia.*—Etter [120] briefly reviews some of the complications of therapeutic artificial hyperpyrexia. Probably the most constant pathologic change seen at necropsy in patients who have succumbed after exposure to high temperatures has been hemorrhage. In most cases the hemorrhages are slight and usually petechial. Parenchymatous degeneration of the liver, in various degrees of severity, also has been present in the majority of cases, frequently together with degeneration of the adrenal glands and hemorrhages into them, as well as various degrees of cerebral edema. Numerous workers have subjected experimental animals to artificial fever. Widespread petechial hemorrhages and hepatic damage have been reported in every instance.

The pathogenesis of hemorrhage in induced fever may be as follows: The elevation of body temperature results in anoxia and a depletion of glycogen in the liver, which in turn results in hepatic damage. With sufficient hepatic damage, there is a decrease in the concentration of prothrombin, with or without a decrease in that of fibrinogen. There is also direct damage to the megakaryocytes with a resulting decrease of circulatory blood platelets. The decrease of platelets, prothrombin and fibrinogen contributes to potential or actual hemorrhage. The inferences from these observations are that extensive hepatic damage is a contraindication to hyperpyrexia, that dextrose should be given routinely both by mouth and parenterally before treatment and that oxygen should be administered routinely throughout all fever sessions. The fall of arterial oxygen tension during fever therapy provides a reasonable explanation for the clinical evidence of oxygen want.

Another serious complication of therapeutic hyperpyrexia is circulatory collapse. This is usually the result of dehydration, with a diminution of blood volume and electrolytes. If an intravenous drip of 5 per cent dextrose in isotonic solution of sodium chloride is started, treatment can sometimes be continued. If the blood pressure continues to fall, however, treatment must be stopped at once. Heat stroke is still another complication of the most serious nature. Apparently there is a derangement of the heat-regulating center, possibly due to anoxemia or to small hemorrhages. In this event, cooling is achieved by tepid sponge baths and a fan, never by ice packs.

*Cystometrogram as a Diagnostic Aid.*—Weyrauch and his co-workers [121] present statistical and clinical data which cast serious doubt on the value of the cystometrogram as a diagnostic test. Forty-seven cystometrograms of normal males between the ages of 20 and 35 years were compared with 25 cystometrograms of hypertonic bladders and an equal number of atonic bladders, chosen at random from groups demonstrating one well defined abnormal condition. In every instance the diagnosis had been fully established on the basis of the history and the results of physical, laboratory and cystoscopic examinations. The determinations were made with a common form of mercury manometer. Despite control of all known variables, great variability was found in the curve of the same person taken at different times. Moreover, the statistical results indicate that the cystometrogram cannot be used to differentiate hypertonic and atonic bladders from the normal in terms of (1) character and slope of the individual curves, (2) the point of terminal injection and (3) the critical pressures. The great variability of cystometrograms in the normal, hypertonic and atonic groups, the broad overlap of the pathologic and the normal, and the fact that numerous abnormal conditions produce identical changes in the curve lead the authors to conclude that "The interpretation of the cystometrogram rests upon the diagnosis, not the diagnosis upon the interpretation of the cystometrogram."

*Cisternal and Lumbar Punctures.*—Reid [122] presents certain points with regard to the indications and dangers associated with lumbar, ventricular and cisternal puncture. The actual technic involved in each procedure is simple so long as the operator has accurate knowledge of the anatomy of the structures that lie in the path of the point of his needle. Of the three procedures, lumbar puncture is the simplest, although if not properly performed it may be dangerous. Ventricular puncture carries a greater risk and should be considered a major operation. Cisternal puncture is an extremely dangerous procedure.

The technical aspects of the cisternal puncture are summarized by Spiegel.[123] The author em-

120. Etter, H. S.: Some Complications of Therapeutic Hyperpyrexia, Arch. Phys. Therapy **25**:154 (March) 1944.

121. Weyrauch, H. M.; Lucia, E. L., and Howard, J.: The Failure of the Cystometrogram as a Diagnostic Test: Clinical Observations and Statistical Analysis, J. Urol. **51**:191 (Feb.) 1944.

122. Reid, W. L.: Lumbar, Ventricular and Cisternal Puncture: Their Indications and Their Dangers, M. J. Australia **1**:311 (April 10) 1943.

123. Spiegel, L.: The Technique of Cisternal Puncture in the Modern Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **28**:96 (Jan.) 1944.

phasizes that this method of obtaining spinal fluid is a procedure for the expert. Its advantage lies in the almost complete absence of postpuncture headache, which is so common with lumbar puncture. In over 10,000 punctures the author has observed no instance of hemorrhage into the cisterna magna. The danger of this occurrence, which is the result of an anomalous course of an artery, has resulted in the abandonment of this procedure for routine use in many clinics.

Commenting on reactions following spinal puncture, an editorialist[124] reviews the various theories of their causation. Leakage of cerebrospinal fluid into the epidural space, meningeal irritation and increased intracranial tension due to reaction of the choroid plexus all have been suggested as the reason for the postpuncture headache. The constitutional makeup of the patient and psychogenic influences are also thought to be contributory factors. Consideration of these several theories and of the contradictory facts presented suggests to the writer that "further studies will be required to elucidate the mechanism of the postpuncture headache and its successful prevention."

In view of the increasing use of spinal anesthesia, Konwaler's[125] study of changes in the spinal fluid following the intrathecal administration of 3 commonly employed anesthetic agents is of interest to syphilologists. The spinal fluids of 31 patients were studied before spinal anesthesia and one, two, and three weeks thereafter. Twenty-four patients received procaine hydrochloride; 3 procaine hydrochloride and tetracaine hydrochloride, and 4 metycaine hydrochloride. Dosage was comparable to that commonly used. Neither cell count nor total protein showed a significant increase; minor changes in the colloidal gold curve were observed in a few cases. No false positive reactions for syphilis occurred.

### SYPHILIS AND PREGNANCY

Rattner[126] has administered the five day drip to 27 pregnant women, 4 of whom had primary syphilis, 15 secondary syphilis, and 8 latent syphilis of less than four years' duration. The majority of the patients were in the fifth month of pregnancy or later, and none of them had received any previous antisyphilitic treatment. Ten patients were given 240 mg. of mapharsen dissolved in 2,000 cc. of 5 per cent dextrose solution daily for five consecutive days. Seventeen patients were given an additional daily intramuscular injection of 2 cc. of a solution of soluble sodium bismuth tartrate, each dose representing 22 mg. of metallic bismuth. One of the 27 patients so treated was lost from observation. In all but 1 of the other 26, pregnancy terminated with the birth of a full term, apparently normal infant; it was believed that 1 mother had been successfully treated for secondary syphilis in the fifth month of pregnancy but had been reinfected or superinfected at a later date.

In addition to the 27 pregnant patients just discussed, there were 5 others who had been treated for early syphilis by the five day drip method and subsequently became pregnant. These women have already been delivered of normal infants, at intervals of twenty, seventeen, eleven, two and ten months after the completion of treatment. It would seem that the efficacy of the five day massive dose method of therapy for syphilis in pregnant women is attested by the fact that normal infants were born in 25 of 26 pregnancies. It is felt that the 1 syphilitic infant was the result of new infection acquired by the mother before the infant was born. Apparently the results of treatment were the same regardless of whether the mother had primary, secondary or early latent syphilis; and the stage of pregnancy did not influence the outcome.

### CONGENITAL SYPHILIS

*Relationship of Congenital Syphilis to Abortion and Miscarriage.*—That the fetus of a syphilitic mother does not become infected before the fourth month has been well established. Dippel[127] has made a study of fetuses of syphilitic and of nonsyphilitic women. A better summary of this paper cannot be had than by quoting the author's conclusions:

1. A series of 68 fetuses of nonsyphilitic and 67 of luetic women were autopsied and certain tissues searched for the presence of spirochetes. Only fetuses which had not reached viability were included in the study.

2. Fetal syphilis was diagnosed upon the discovery of spirochetes in fetal organs. No other criterion was considered reliable for the diagnosis from autopsy material.

3. Spirochetes were generally found in largest number in the perivascular tissues of liver and lungs. Long bones, placenta, and umbilical cord were least satisfactory for the search of spirochetes.

124. Reactions Following Spinal Puncture, editorial, J. A. M. A. **123**:355 (Oct. 9) 1943.

125. Konwaler, B. E.: Changes in the Cerebrospinal Fluid Following Spinal Anesthesia, Am. J. Clin. Path. **13**:378 (July) 1943.

126. Rattner, H.: The Treatment of Syphilis in Pregnancy by the Five-Day Massive Dose Method, Am. J. Obst. & Gynec. **46**:255 (Aug.) 1943.

127. Dippel, A. L.: The Relationship of Congenital Syphilis to Abortion and Miscarriage, and the Mechanism of Intrauterine Protection, Am. J. Obst. & Gynec. **47**:369 (March) 1944.

4. The characteristic morphology of the *S. pallida* was not found in three macerated fetuses from missed abortions. That the observed structures were dead or dying spirochetes was proved by comparison with the changing morphology in an aging darkfield preparation.

5. No spirochetes were found in the stained preparations from the 68 fetuses of nonsyphilitic women.

6. Spirochetes found in the tissues of fetuses from luetic mothers (cases in which the blood Wassermann was positive as well as those in which serology had been rendered negative by therapy) were morphologically like the *S. pallida* and were considered as such since no spirochetes of any form were seen in the fetuses of nonluetic mothers.

7. Spirochetes were found in 16 of 67 fetuses of leutic mothers, an incidence of 23.9 per cent, which is the demonstrable role played by syphilis in the production of abortion and miscarriage in this series.

8. Spirochetes were discovered in 14 of 42 fetuses of Wassermann positive mothers, or in 33.2 per cent, and in two of nine fetuses of Wassermann negative mothers, 22.2 per cent, reaffirming that negative serology following antiluetic therapy is no assurance against congenital syphilis.

9. Spirochetes were not found in fetal tissues prior to the eighteenth week of gestation, i. e., in the abortion period. The incidence of fetal infection with spirochetes was found to rise from 10 per cent in the first one-half of the miscarriage period to 50 per cent in the latter one-half of that period with the highest incidence (66.7 per cent) in the twenty-sixth week. Appropriate conclusions relative to the role played by syphilis in terminating pregnancies before viability are drawn.

10. The limited material of this study suggests that there is some natural protection of the fetus against syphilis during the first 17 weeks of pregnancy. However, Wassermann positive mothers must receive therapy before the eighteenth week if their fetuses are to be guarded against syphilitic infection, and both Wassermann positive and negative gravida must have therapy before the twenty-third week or approximately 50 per cent of their fetuses can be expected to be infected before viability is reached. This confirms the modern teaching that antisyphilitic treatment must be started early in pregnancy and certainly before the eighteenth week of gestation.

11. Evidence is offered to show that the Langhans layer of chorionic epithelium affords appreciable protection of the fetus against the invasion of the *S. pallida*, even after the sixteenth gestational week. At this late stage, it is in the form of delayed delamination and differentiation of the Langhans cells.

*Tooth Buds and Jaws.*—Bauer[128] reports a study by histologic methods of the tooth buds and jaws of 4 fetuses and 2 infants with congenital syphilis. T. pallidum was demonstrated throughout the bony structure of the tooth and jaw but was particularly numerous about and within the tooth buds, a site of intense growth activity. Tissue reaction in the form of plasma cells and fibrosis lagged behind the appearance of masses of spirochetes, and did not reach a maximum until after birth. No evidence of any systemic disturbance of calcification such as occurs in rickets was found in the cases studied. Bauer believes that the chronic syphilitic inflammation of the tooth sac produces the enamel hypoplasia of the deciduous teeth and, by pressure on the early tooth bud, results in the characteristic distortion of the crown of the permanent teeth (Hutchinson incisor, mulberry molar).

*Interstitial Keratitis.*—Troedsson[129] presents 6 cases of interstitial keratitis of congenital syphilis treated with artificial fever therapy. In 2 cases the temperature never reached 105 F. In 2 cases it was 105 F. for only short periods. In 2 cases it was over 105 F. for a considerable period. The result was excellent in all cases. The author concludes that low temperatures, that is, 100 to 104 F., are satisfactory. Treatments may be given while the patient is ambulatory.

Perritt[130] presents the evolutionary stages through which his work on corneal transplantation has passed. The source of the transplant is usually: (1) a freshly enucleated eye of a living human being; (2) a cornea obtained from a stillborn infant, or (3) a cornea obtained from an infant who has died a few hours or a few days after birth. The important considerations in the source of material are: that the epithelium be normal; that there be no edema, blebs or vesicles, and, especially, that the endothelium be normal. Corneas may be preserved for a period of time up to forty-eight hours with a minimal amount of change to the epithelial and endothelial tissues. They are usually kept in a sterile jar, resting on a sterile cotton which is saturated with isotonic solution of sodium chloride. The cornea faces upward. These jars are stored in a refrigerator the temperature of which is 2 to 4 C. The indications and contraindications for corneal transplantation are discussed. In interstitial keratitis a good operative result may be obtained if the Wassermann reaction is negative and the eye "quiet," with a central superficial or deep leukoma and without underlying pathologic change in the iris or synechias.

128. Bauer, W. B.: Tooth Buds and Jaws in Patients with Congenital Syphilis: Correlation Between Distribution of Treponema Pallidum and Tissue Reaction, Am. J. Path. **20**:297 (March) 1944.

129. Troedsson, B. S.: Syphilitic Keratitis Treated with Physically Induced Fever: Report of Six Cases with Excellent Results, Arch. Phys. Therapy **24**:401 (July) 1943.

130. Perritt, R. A.: Corneal Transplantation, Arch. Ophth. **30**:14 (July) 1943.

# ANTITHYROID DRUGS, WITH PARTICULAR REFERENCE TO THIOURACIL

ROBERT H. WILLIAMS, M.D.

BOSTON

In the last few years a great deal of progress has been made in elucidating the physiology of the thyroid gland and in establishing some of the relationships of its function to the pituitary gland and the body cells. As a result of this progress thyrotoxicosis is treated with greater effectiveness. The drugs which have been of greatest aid are iodine, cyanides, thiocyanates, sulfonamide compounds and thioureas. Since these substances inhibit the function of the thyroid gland, they are spoken of as antithyroid drugs. This is true in spite of the fact that they may increase the work of the gland, as evidenced by the marked hyperplasia and hypertrophy which they produce in the thyroid.

## IODINE

The effectiveness of iodine in the treatment of goiter was described more than a hundred years ago by Coindet.[1] Nevertheless, its popularization in the treatment of toxic goiter was brought about by Plummer [2] only two decades ago. This drug has afforded great aid in the treatment of thyrotoxic patients. However, sometimes the thyrotoxicosis is refractory to iodine, either at the beginning of treatment or after prolonged iodide therapy. In many patients there is only partial improvement. The obscurity of the exact action of iodide in the treatment of hyperthyroidism, as well as the desire for a drug with stronger antithyroid action, has maintained keen interest in the study of varied substances exerting an effect on the thyroid gland.

The use of radioactive iodine has helped elucidate the physiology of the thyroid gland.[3] Iodine becomes concentrated in the thyroid within a few minutes after its ingestion. The glands of patients with untreated toxic diffuse (exophthalmic) goiter have a particularly great avidity for iodine. These observations have led some investigators [4] to treat thyrotoxic patients with radioactive iodine; its therapeutic effectiveness depends on the irradiation of the thyroid tissue by the radioactive iodine concentrated within it.

## CYANIDES

It is a well established fact that a deficiency of iodine in the body will produce a goiter. Such deficiency may be the result of a low iodine intake or of ingestion of substances, such as calcium salts, which interfere with iodine metabolism. The goitrogenic effect of cabbage, described by Chesney, Clawson and Webster,[5] is presumably on an iodine deficiency basis. A

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. Coindet, cited by Means, J. H.: Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937, p. 331.

2. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, J. A. M. A. **80**:1955 (June 30) 1923.

3. (*a*) Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**:510 (May) 1938. (*b*) Hamilton, J. G., and Soley, M. H.: Studies in Iodine Metabolism by the Use of New Radioactive Isotope of Iodine, Am. J. Physiol. **127**:557 (Oct.) 1939. (*c*) Hamilton, J. G.; Soley, M. H., and Eichorn, K. B.: Deposition of Radioactive Iodine in Human Thyroid Tissue, Univ. Calif. Publ., Pharmacol. **1**:339, 1940. (*d*) Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: III. Iodine Collection as a Criterion of Thyroid Function in Rabbits Injected with Thyrotropic Hormone, Endocrinology **29**:82 (July) 1941. (*e*) Mann, W.; Leblond, C. P., and Warren, S. L.: Iodine Metabolism of the Thyroid Gland, J. Biol. Chem. **142**: 905 (Feb.) 1942. (*f*) Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation **21**:25 (Jan.) 1942. (*g*) Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: V. The Use of Radioactive Iodine in the Differential Diagnosis of Two Types of Graves' Disease, ibid. **21**:31 (Jan.) 1942.

4. (*a*) Hertz, S., and Roberts, A.: The Application of Radioactive Iodine in the Therapy of Graves' Disease, J. Clin. Investigation **21**:624 (Sept.) 1942. (*b*) Hamilton, J. G., and Lawrence, J. H.: Recent Clinical Developments in the Therapeutic Application of Radio-Phosphorus and Radio-Iodine, ibid. **21**:624 (Sept.) 1942.

5. Chesney, A. M.; Clawson, T. A., and Webster, B.: Endemic Goitre in Rabbits: I. Incidence and Characteristics, Bull. Johns Hopkins Hosp. **43**:261 (Nov.) 1928.

lowering of the basal metabolic rate [6] is associated with the goitrogenic effect. Iodine exerts an inhibitory effect [7] on the goitrogenic and hypometabolic effects of a cabbage diet. Marine and his co-workers [8] showed that all of the Brassicae tested produced goiters. Since these plants contain organic cyanides and since cyanides inhibit tissue oxidations the goitrogenic properties of various cyanides were studied. Methyl cyanide was more active than any of the other cyanides tested. Spence [9] stated that the goitrogenic action of the cyanides is due to the liberation of hydrocyanic acid in the body; the slower the liberation the more goitrogenic effect do they have. Sodium thiocyanate and sodium cyanide were relatively inactive. Spence cast doubt as to whether cyanide was the substance in cabbage responsible for the production of goiter.

### THIOCYANATES

It has been observed [10] that goiters developed in some patients receiving thiocyanate therapy for hypertension. Of 246 patients so treated by Barker and associates,[10a] 11 were found to have goiters. Nine had myxedematous facies, and their basal metabolic rates ranged around — 10 per cent. Iodide exerts a prophylactic effect, and thyroid abolishes the goiter in spite of continued thiocyanate treatment. Fahlund [10b] reported the development of acute thyroiditis in a patient receiving thiocyanate treatment for hypertension. Rawson, Hertz and Means [10f] reported 2 patients with a large goiter, hypothyroidism, exophthalmos (in 1 case), "increased urinary excretion of thyrotropic hormone in the inactivated form", and low protein-bound iodine concentration in the plasma, all of which changes developed during thiocyanate therapy. After the administration of radioactive iodine to 1 patient, a smaller proportion than normal was excreted. The patient resembled thyrotoxic subjects in this regard, and a biopsy of the thyroid gland showed marked hyperplasia; the architecture in some areas resembled "papillary cystadenoma." Estimations of the amount of radioactive iodine, made on the thyroid tissue removed at biopsy, showed that the major part of the iodine had gone to the thyroid gland. It was concluded that thiocyanates act on the thyroid gland in such a manner as to interfere with the manufacture of the thyroid hormone; a decrease in the circulating thyroid hormone results, and, in turn, there is an increased production of thyrotropic hormone, which leads to hypertrophy of the thyroid gland.

Rawson, Tannheimer and Peacock [11] produced goiters in rats by the administration of a thiocyanate. The thyroid glands of these animals had a much greater avidity for radioactive iodine than did the glands of the untreated control rats.

In spite of the antithyroid action of thiocyanates these drugs have not been utilized in the treatment of thyrotoxicosis.

### THIOUREAS AND SULFONAMIDE COMPOUNDS

Interest in the goitrogenic action of Brassicae was resumed when Kennedy and Purves [12] sought the mechanism by which brassica seeds produced goiters. They noted that these seeds produced large goiters in rats in spite of the simultaneous administration of large doses of iodide. Sections of the thyroid gland from rats so treated showed marked hyperplasia of the acinar cells with diminution of the colloid.

Griesbach [13] demonstrated that rats treated with brassica seeds experienced a rapid increase in the basophilic cells of the pituitary and a decrease in the acidophilic cells. No goitrogenic

6. Webster, B.; Clawson, T. A., and Chesney, A. M.: Endemic Goitre in Rabbits: II. Heat Production in Goitrous and Non-Goitrous Animals, Bull. Johns Hopkins Hosp. **43**:278 (Nov.) 1928.

7. Webster, B., and Chesney, A. M.: Endemic Goitre in Rabbits: III. Effect of the Administration of Iodine, Bull. Johns Hopkins Hosp. **43**:291 (Nov.) 1928.

8. (*a*) Marine, D.; Baumann, E. J., and Cipra, A.: Studies on Simple Goiter Produced by Cabbage and Other Vegetables, Proc. Soc. Exper. Biol. & Med. **26**: 822 (June) 1929. (*b*) Marine, D.; Baumann, E. J.; Spence, A. W., and Cipra, A.: Further Studies on the Etiology of Goiter with Particular Reference to the Action of Cyanides, ibid. **29**:772 (March) 1932.

9. Spence, A. W.: Researches on the Aetiology of Goiter, St. Barth. Hosp. Rep. **67**:201, 1934.

10. (*a*) Barker, M. H.; Lindberg, H. A., and Wald, M. H.: Further Experiences with Thiocyanates: Clinical and Experimental Observations, J. A. M. A. **117**:1591 (Nov. 8) 1941. (*b*) Fahlund, G. T. R.: Painful Enlargement of Thyroid Gland, Manifestation of Sensitivity to Thiocyanate, Proc. Staff Meet., Mayo Clin. **17**:289 (May 13) 1942. (*c*) Kolbacher, J. L.: Production of Goiter and Myxedema by Sulfocyanates, Ohio State M. J. **38**:541 (June) 1942. (*d*) Foulger, M. P. H., and Rose, E.: Acute Goiter During Thiocyanate Therapy for Hypertension, J. A. M. A. **122**: 1072 (Aug. 14) 1943. (*e*) Rawson, R. W.; Hertz, S., and Means, J. H.: Cyanate Goiter in Man, J. Clin. Investigation **24**:624 (Sept.) 1942; (*f*) Cyanate Goiter in Man, Ann. Int. Med. **19**:829 (Dec.) 1943.

11. Rawson, R. W.; Tannheimer, J. F., and Peacock, W.: The Uptake of Radioactive Iodine by the Thyroids of Rats Made Goiterous by Potassium Thiocyanate and by Thiouracil, Endocrinology **34**:245 (April) 1944.

12. Kennedy, T. H., and Purves, H. D.: Studies on Experimental Goitre: I. The Effect of Brassica Seed Diets on Rats, Brit. J. Exper. Path. **22**:241 (Oct.) 1941.

13. Griesbach, W. E.: Studies on Experimental Goitre: II. Changes in the Anterior Pituitary of the Rat, Produced by Brassica Seed Diet, Brit. J. Exper. Path. **22**:245 (Oct.) 1941.

effect was observed [14] in rats previously subjected to hypophysectomy. This indicates that in order "to produce thyroid hyperplasia it requires the mediation of the thyrotropic hormone of the pituitary". Hyperplasia previously induced by feeding brassica seeds rapidly regressed after hypophysectomy despite continued feeding of the seeds. Kennedy [15] suspected that the goitrogenic principle in these seeds was a thiourea derivative, and on testing allyl thiourea and thiourea he found each to exert a marked effect.

Richter and Clisby,[16] in the course of studying the effect of bitter-tasting substances in rats, discovered that phenylthiocarbamide, a thiourea derivative, caused marked hypertrophy of the thyroid. The acinar cells were tall and columnar, and there was very little colloid. Phenylthiocarbamide was found to be extremely toxic; many rats died of pulmonary edema and hydrothorax. In some rats, after prolonged treatment the epithelial cells were found to have become dislodged and to have almost completely filled the lumens. These changes were interpreted as representing a state of exhaustion in the thyroid.

Mackenzie, Mackenzie and McCollum [17] observed, while studying the effects of large doses of sulfaguanidine on the nutritional status of rats, that great enlargement of the thyroid gland resulted. There were marked hyperplasia and hypertrophy of the acinar cells and a depletion of colloid. These studies were extended to include the effect of a large number of sulfonamide compounds, thioureas and related compounds.[18] Goitrogenesis has been induced by a sulfonamide or thiourea substance, or both, in rats,[18a] mice,[18b] dogs,[18b] rabbits,[19] chicks [20] and human beings,[21] but most of the studies have dealt with rats. The goitrogenic effect is more pronounced in young rats than in older ones. Goiters have been produced with one of the thiourea substances in rats in utero [22] and in others during the first few days of life, the only source of the drug being mammary transmission.[23]

With the sulfonamide compounds and thioureas used by the Mackenzies and by Astwood and associates [18d] the effect on the pituitary-thyroid axis was quantitative and not qualitative. Sulfadiazine was the most goitrogenic of the sulfonamide compounds tested. The thioureas were more active than the sulfonamide compounds, and thiouracil (2-thio-6-oxyprimidine) was the most goitrogenic of more than one hundred compounds tested by Astwood.[18d]

*Anatomic and Physiologic Effects.*—The chief anatomic alterations induced by the thioureas and sulfonamide compounds have involved body size, the thyroid gland and the pituitary gland. The rate of growth was readily inhibited when young animals were fed one of these substances. Cretinism was produced in rats,[22a] and metamorphosis was retarded in tadpoles.[24] Thiouracil inhibited the growth-promoting effect of anterior pituitary growth hormone injected into rats.[23b] The thyroid glands of rats treated with thiourea or a sulfonamide compound showed distinct enlargement within a few days after the beginning of the treatment. For example, Astwood and Bissell [25] found that seventy-two hours after thiouracil therapy was begun on rats there was a 50 per cent increase in the weight of the thyroid gland. The gain in weight continued rapidly for the next five days, and by the end of two weeks there was a threefold increase.

14. Griesbach, W. E.; Kennedy, T. H., and Purves, H. D.: Studies on Experimental Goitre: III. The Effect of Goitrogenic Diet on Hypophysectomized Rats, Brit. J. Exper. Path. **22**:249 (Oct.) 1941.

15. Kennedy, T. H.: Thioureas as Goitrogenic Substances, Nature, London **150**:233 (Aug. 22) 1942.

16. Richter, C. P., and Clisby, K. H.: Toxic Effects of Bitter Tasting Phenylthiocarbamide, Arch. Path. **33**: 46 (Jan.) 1942.

17. Mackenzie, J. B.; Mackenzie, C. G., and McCollum, E. V.: Effect of Sulfanilylguanidine on the Thyroid of the Rat, Science **94**:518 (Nov. 28) 1941.

18. (*a*) Mackenzie, J. B., and Mackenzie, C. G.: The Effect of "Sulfa" Drugs on the Thyroid Gland in Rats and Mice, Federation Proc. **1**:22, 1942. (*b*) Mackenzie, C. G., and Macknezie, J. B.: Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism, Endocrinology **32**:185 (Feb.) 1943. (*c*) Astwood, E. B.; Sullivan, J.; Bissell, A., and Tyslowitz, R.: Action of Certain Sulfonamides and of Thiourea upon the Function of the Thyroid Gland of the Rat, ibid. **32**:201 (Feb.) 1943. (*d*) Astwood, E. B.: The Chemical Nature of Compounds Which Inhibit the Function of the Thyroid Gland, J. Pharmacol. & Exper. Therap. **78**:79 (May) 1943. (*e*) Mackenzie, J. B., and Mackenzie, C. G.: Effect of Prolonged and Intermittent Sulfonamide Feeding on the Basal Metabolic Rate, Thyroid and Pituitary, Bull. Johns Hopkins Hosp. **74**: 85 (Feb.) 1944.

19. Baumann, E. J.; Metzger, N., and Marine, D.: Mode of Action of Thiourea on the Thyroid Gland of Rabbits, Endocrinology **34**:44 (Jan.) 1944.

20. Mixner, J. P.; Reineke, E. P., and Turner, C. W.: Effect of Thiouracil and Thiourea on the Thyroid Gland of the Chick, Endocrinology **34**:168 (March) 1944.

21. Williams, R. H.: Unpublished data.

22. (*a*) Hughes, A. M.: Cretinism in Rats Induced by Thiouracil, Endocrinology **34**:69 (Jan.) 1944. (*b*) Williams, R. H.: Further Studies on the Absorption, Distribution and Elimination of Thiouracil, to be published.

23. (*a*) Hughes.[22a] (*b*) Williams, R. H.; Weinglass, A. R.; Bissell, G. W., and Peters, J. B.: Anatomical Effects of Thiouracil, Endocrinology **34**: 317 (May) 1944.

24. Hughes, A. M., and Astwood, E. B.: Inhibition of Metamorphosis in Tadpoles by Thiouracil, Endocrinology **34**:138 (Feb.) 1944.

25. Atwood, E. B., and Bissell, A.: Effect of Thiouracil on the Iodine Content of the Thyroid Gland, Endocrinology **34**:282 (April) 1944.

Cessation of the drug therapy after eight days was followed by a rapid decrease in the size of the gland; a normal size was reached in seven days. The enlarged thyroids were vascular. The cells were tall and columnar, and the colloid was greatly decreased in amount. The intrafollicular colloid exhibited a decrease in its fluorescence, indicating its low content of iodine.[26] The Mackenzies [18b] found that the sulfonamide compounds and thioureas produced changes in the pituitary gland consisting of degranulation and decrease in the number of acidophils, vacuolation and increase in number and size of the basophils. These changes, which occurred as early as the fourteenth day, simulated those reported following thyroidectomy.[27] The effects of the thioureas and sulfonamide compounds on body growth, the pituitary gland and the thyroid gland presumably result from a decrease in the quantity of thyroid hormone produced, since these changes can be prevented by the simultaneous administration of thyroxin or desiccated thyroid.[28] In fact, the maintenance or restoration of normal weight of the thyroid by the administration of thyroxin to rats simultaneously treated with thiouracil has been used [29] to assay the quantity of thyroid hormone produced under various environmental conditions. Chicks have also been shown [20] to be suitable for the same type of estimation. The administration of iodide or diiodotyrosine does not prevent these effects,[28] nor do injections of thyrotropic hormone.[23b] No goitrogenesis results in hypophysectomized rats fed sulfonamide compounds or thioureas.

Sulfonamide compounds and thioureas have been shown to decrease the basal oxygen consumption of rats.[28] Estimations of the oxygen consumption of slices of tissues ($QO_2$) from rats previously treated with thiouracil showed an increase in the $QO_2$ of thyroid tissue, while the $QO_2$ of adrenal, liver and muscle slices was essentially normal.[30]

Thiouracil was found not to inhibit the effect of chorionic gonadotropin.[23b] The adrenomegalic activity of the adrenotropic hormone was augmented rather than inhibited, and the goitrogenic effects of thyrotropin were supplemented.[23b]

Microscopic examination of essentially all of the tissues of many rats treated with 0.25 per cent thiouracil in the drinking water for four weeks or longer failed to show any abnormalities, other than in the thyroid.[23b] Meyer, Collins and Marine,[31] using very large quantities of thiouracil, observed toxic reactions in some rats, consisting of cachexia, tremor, convulsions, bloody urine and feces, edema of the lungs and "damage" to the liver and kidney. Mackenzie and Mackenzie [32] observed that pulmonary edema developed in some of their animals receiving thiourea.

Anemia and leukopenia with neutropenia have been observed in association with the administration of large quantities of thiouracil [23] or thiourea [33] to rats. The simultaneous administration of "solubilized" liver was found to protect against the changes induced by thiourea. There is no report of the use of any such substance in the protection against the toxic effects of thiouracil.

*Iodine Metabolism.*—Gersh [34] demonstrated a reduction in the organic iodine content of the colloid in rats treated with sulfaguanidine which is detectable as early as the second day of treatment. Thiourea fed to rabbits caused a rapid decrease in the thyroxin and nonthyroxin iodine content of the thyroid.[19]

Astwood and Bissell [25] found that the administration of thiouracil to young rats was followed by a nearly complete disappearance of iodine from the thyroid glands in five days. This effect was inhibited by hypophysectomy or by the injection of thyroxin. Withdrawal of the drug after eight days was followed by reaccumulation of iodine; however, injections of thyroxin or removal of the pituitary markedly retarded the reaccumulation of iodine. Thyrotropin delayed slightly the loss of iodine from the thyroid glands of rats treated concurrently with thiouracil.

26. Dempsey, E. W.: Fluorescent and Histochemical Reactions in the Rat Thyroid at Different States of Physiological Activity, Endocrinology **34**:27 (Jan.) 1944.

27. Zeckwer, I. T.; Davison, L. W.; Keller, T. B., and Livingood, C. S., Jr.: The Pituitary in Experimental Cretinism: I. Structural Changes in the Pituitaries of Thyroidectomized Rats, Am. J. M. Sc. **190**: 145 (Aug.) 1935.

28. (*a*) Mackenzie and Mackenzie.[18b] (*b*) Astwood, Sullivan, Bissell and Tyslowitz.[18c]

29. Dempsey, E. W., and Astwood, E. B.: Determination of the Rate of Thyroid Hormone Secretion at Various Environmental Temperatures, Endocrinology **32**:509 (June) 1943.

30. Jandorf, B. J., and Williams, R. H.: Effects of Oral Administration of Thiouracil on the Metabolism of Isolated Tissues from Normal and Hyperthyroid Rats, Am. J. Physiol. **141**:91 (March) 1944.

31. Meyer, A. E.; Collins, M. B., and Marine, D.: Toxicity of Thiouracil in Normal and Thyroidectomized Rats, Proc. Soc. Exper. Biol. & Med. **55**:221 (March) 1944.

32. Mackenzie, J. B., and Mackenzie, C. G.: Production of Pulmonary Edema by Thiourea in the Rat and Its Relation to Age, Proc. Soc. Exper. Biol. & Med. **54**:34 (Oct.) 1943.

33. Goldsmith, E. D.; Gordon, A. S.; Finkelstein, G., and Charipper, H. A.: Suggested Therapy for Prevention of Granulocytopenia Induced by Thiourea, J. A. M. A. **125**:847 (July 22) 1944.

34. Cited by Mackenzie and Mackenzie.[18b]

In vitro, as well as in vivo, experiments indicate [35] that in the presence of thioureas and sulfonamide compounds, except sulfanilamide, the thyroid tissue removes a distinctly subnormal amount of radioactive iodine from the fluid in which it is bathed. Furthermore, only a small proportion of the iodine extracted is converted into diiodotyrosine or thyroxin. Most of the administered iodine is readily excreted in the urine.

Even seven days after discontinuation of thiouracil therapy of rats the capacity of the thyroid gland to concentrate radioactive iodine and to convert it to diiodotyrosine and thyroxin was depressed.[35d] However, the gland became normal in these respects two weeks after the use of thiouracil was discontinued. Although sulfanilamide strongly inhibits the in vitro conversion of radioactive iodine to thyroxin and diiodotyrosine, it has little effect on the iodine-concentrating capacity of thyroid tissue.[35c] Sodium azide provokes a response similar to the one exhibited by sulfanilamide. This indicates that in thyroid tissue there exists a mechanism for concentrating iodine that does not depend on its conversion to thyroxin and diiodotyrosine.

Whether the thioureas and sulfonamide compounds inhibit the manufacture of thyroxin in extrathyroid sites has not been demonstrated; that such a manufacture may take place under normal conditions has been indicated.[36]

Several thyroid glands of thyrotoxic patients treated with thiouracil for a few weeks were found to have only very small quantities of thyroxin iodine.[37] The protein-bound iodine content of the plasma is reduced to normal limits with thiouracil therapy.[38]

Neither the sulfonamide compounds nor the thioureas interfere with the effect of thyroxin in elevating the basal metabolic rate.[39] Thiouracil was demonstrated not to interfere with the breakdown of desiccated thyroid when fed to normal subjects.[37]

*Effect of Thiouracil on the Activity of Certain Enzymes.*—Recent studies [40] have indicated a possible mechanism of conversion of diiodotyrosine to thyroxin. Johnson and Tewkesbury [40a] suggested that thyroxin may be formed by the oxidative coupling of 2 molecules of diiodotyrosine, by a mechanism analogous to the oxidation of paracresol by potassium ferricyanide. Westerfeld and Lowe [40b] intimated that a biologic synthesis may be produced by peroxidase. Dempsey,[26] using a peroxide-benzidine staining technic for slices of thyroid, showed that the addition of thiouracil to the staining mixture prevented the formation of blue granules in the follicular cells. Quantitative estimations by the method of Bancroft and Elliott [41] of the peroxidase content of thyroid tissues have shown [21] that thiouracil tends to cause a reduction in peroxidase activity no matter whether it is injected intravenously or whether it is added to a suspension of thyroid tissue in vitro.

Thiouracil has not been found [26] to exert an effect on the cytochrome oxidase activity of the thyroid. It does not inhibit the action of xanthine oxidase or of triosephosphate-dehydrogenase [42] but does inhibit tyrosinase.[43]

*Absorption of Thiouracil from the Gastrointestinal Tract, Its Distribution Throughout the Body and Its Fate.*—Thiouracil is a white crystalline substance with no odor, but it has a bitter taste. It is readily soluble in sodium hydroxide, but it is only moderately soluble in water. Meth-

35. (*a*) Keston, A. S.; Goldsmith, E. D.; Gordon, A. S., and Charipper, H. A.: The Effect of Thiourea upon the Metabolism of Iodine by Rat Thyroid, J. Biol. Chem. **152**:241 (Feb.) 1944. (*b*) Franklin, A. L., and Chaikoff, I. L.: Effect of Sulfonamides on the Conversion in Vitro of Inorganic Iodide to Thyroxins and Diiodotyprosine by Thyroid Tissue with Radioactive Iodine as Indicator, ibid. **152**:295 (Feb.) 1944. (*c*) Schachner, H.; Franklin, A. L., and Chaikoff, I. L.: On the in Vitro Accumulation of Inorganic Iodide by Surviving Thyroid Tissue with Radioactive Iodine as Indicator, Endocrinology **34**:159 (March) 1944. (*d*) Franklin, A. L.; Lerner, S. T., and Chaikoff, I. L.: The Effect of Thiouracil on the Formation of Thyroxine and Diiodotyrosine by the Thyroid Gland of the Rat with Radioactive Iodine as Indicator, ibid. **34**:365 (April) 1944. (*e*) Rawson, Tannheimer and Peacock.[11]

36. (*a*) Chapman, A.: Extrathyroidal Iodine Metabolism, Endocrinology **29**:686 (Nov.) 1941. (*b*) Morton, M. E.; Chaikoff, I. L.; Reinhardt, W., and Anderson, E.: Radioactive Iodine as Indicator of Metabolism of Iodine: Formation of Thyroxin and Diiodotyrosine by Completely Thyroidectomized Animal, J. Biol. Chem. **147**:757 (March) 1943.

37. Williams, R. H., and Clute, H. M.: Thiouracil in the Treatment of Thyrotoxicosis: A Report of Seventy-Two Cases, New England J. Med. **230**:657 (June 1) 1944.

38. (*a*) Williams and Clute.[37] (*b*) Watson, E. M., and Wilcox, L. D.: Thiouracil in the Treatment of Thyrotoxicosis, Canad. M. A. J. **51**:29 (July) 1944.

39. (*a*) Mackenzie and Mackenzie.[18b] (*b*) Astwood, Sullivan, Bissell and Tyslowitz.[18c] (*c*) Williams, R. H., and Bissell, G. W.: Thiouracil in the Treatment of Thyrotoxicosis, New England J. Med. **229**:97 (July 15) 1943.

40. (*a*) Johnson, T. B., and Tewkesbury, L. B.: The Oxidation of 3-5-Diiodotyrosine to Thyroxine, Proc. Nat. Acad. Sc. **28**:72, 1942. (*b*) Westerfeld, W. W., and Lowe, C.: The Oxidation of p-Cresol by Peroxidase, J. Biol. Chem. **145**:463 (Oct.) 1942.

41. Bancroft, G., and Elliott, K. A. C.: The Distribution of Peroxidase in Animal Tissues, Biochem. J. **28**:1911, 1934.

42. Jandorf, B. J.: Unpublished data.

43. Paschkis, K.: Read at the meeting of the Association for the Study of Internal Secretions, Chicago, June 12, 1944.

ods [44] for the estimation of thiouracil in the body fluids and tissues are based on Grote's observation [45] that a blue color was formed by substances of a C-S type when treated with a special reagent. Grote's reagent is produced by the treatment of sodium nitroferricyanide in sodium bicarbonate solution with hydroxylamine hydrochloride followed by bromine. This color reaction has been used for the estimation of thiouracil in studies conducted [46] on man and on rats concerning what happens to the drug in the body. It rapidly disappears from the gastrointestinal tract, most of it being absorbed within two hours. The major portion of the absorption probably occurs in the stomach and duodenum, since thiouracil appears in the blood in appreciable quantity very rapidly and inasmuch as only a small proportion of the drug has been found distal to the duodenum. The duodenum and jejunum can absorb thiouracil very rapidly as shown when these segments are isolated and the drug is injected into them. No thiouracil is excreted in the stools, but some of it is broken down in the gastrointestinal tract. The contents of the stomach, duodenum and jejunum exhibit a destructive action when incubated with the drug in vitro; the ileal contents cause no destruction. Approximately 15 per cent of the usual clinical dose of thiouracil, 0.1 or 0.2 Gm., is destroyed in the gastrointestinal tract. The remainder is distributed throughout essentially all of the tissues and fluids of the body. The blood cells contain several times as much as does the plasma, and the red cells possess a greater total quantity than do the white cells. Lymphocytes, as well as granulocytes, carry thiouracil. The pituitary, thyroid, adrenals and bone marrow acquire a greater concentration than the other tissues, while the skin and muscle contain less. In most tissues the concentration of thiouracil is several times that in the blood. Milk possesses a greater concentration than do the other body fluids. A transplacental transmission of thiouracil has been demonstrated.[22b]

Frequent estimations, throughout twenty-four hour intervals, of the concentration of thiouracil in the blood of persons receiving routine therapeutic doses of the drug show a marked lability, a sharp increase in the concentration occurring within an hour or two after each dose. During the subsequent few hours a steady decline results. After an interval of eight hours elapses, a decided decrease in the concentration results, and after intervals of twelve to twenty-four hours, little or none of the drug is found in the urine. The concentration of thiouracil in the urine shows fluctuations comparable to those in the blood. Frequent small doses of thiouracil maintain greater constancy in the blood and urine levels than do equivalent daily amounts administered less frequently. A larger quantity of the drug is excreted when 0.2 Gm. is given once or twice daily than when one half of this dose is given twice as often. About twenty-four hours after discontinuation of therapy the quantity of thiouracil is very small, and after three days no thiouracil is usually demonstrable in the blood or urine.

Estimations of the total excretion of thiouracil by many patients, with or without thyroid disease, who were receiving from 0.2 to 1.2 Gm. of the drug daily showed [46a] that about one third was excreted in the urine. Persons with severe damage to the kidneys excreted very little thiouracil in the urine, but the concentration in the blood was not different from that in subjects with normal renal function. The liver was suspected of breaking down large quantities of thiouracil, but persons with advanced cirrhosis of the liver acquired no greater concentration of the drug in the blood than did normal persons.

Freshly cut slices of many tissues tested were shown to break down thiouracil. When calculated on a weight basis pituitary tissue was the most active one in destroying the drug, thyroid and adrenal were next, while muscle and pancreas were least active. It was estimated [22b] that with the usual therapeutic doses of thiouracil, 0.1 to 0.6 Gm. daily, approximately 50 per cent of the drug was broken down in the body, excluding the amount broken down in the gastrointestinal tract. The specific breakdown products of thiouracil have not been identified. Studies of sulfur balance demonstrated an increased excretion of neutral sulfur in the urine when the patients were given thiouracil, but there were no changes as regards the excretion of cysteine, cystine, thiourea, thiocyanate, thiosulfate, urochrome or melanin. Furthermore, uracil was not found in the urine.

In guinea pigs it has been shown [47] that the administration of anterior pituitary thyrotropin decreased the amount of thiouracil stored in the thyroid gland. On the other hand, potassium

44. Williams, R. H.; Jandorf, B. J., and Kay, G. A.: Methods for the Determination of Thiouracil in Tissues and Body Fluids, J. Lab. & Clin. Med. **29**:329 (March) 1944.

45. Grote, I. W.: A New Color Reaction for Soluble Organic Sulfur Compounds, J. Biol. Chem. **93**:25, 1931.

46. (*a*) Williams, R. H.; Kay, G. A., and Jandorf, B. J.: Thiouracil: Its Absorption, Distribution and Excretion, J. Clin. Investigation, to be published. (*b*) Williams.[22b]

47. Williams, R. H.; Weinglass, A. R., and Kay, G. A.: Thiouracil Storage in the Thyroid as Affected by Thyrotropic Hormone and Potassium Iodide, Am. J. M. Sc. **207**:701 (June) 1944.

iodide increased its storage. The first observation suggested that a larger amount of thiouracil was necessary to establish a given concentration of the drug in the thyroid with hyperthyroidism than with euthyroidism; this has been shown to be the case clinically. However, it has not been found [48] clinically that there was a decrease in the requirement for thiouracil when potassium iodide was used simultaneously.

*Thiouracil in the Treatment of Thyrotoxicosis.*—Following Astwood's introduction of thiourea and thiouracil in the treatment of thyrotoxicosis, thiourea has not been used much [49]; it is not as satisfactory as thiouracil, since it gives a disagreeable odor to the breath, tends to cause more gastrointestinal disturbance and does not have so strong an antithyroid action.

Whereas only about 201 patients have been reported [50] as having been treated with thiouracil, actually there have probably been more than 2,000. It has not been necessary to hospitalize most patients during treatment, but it is important to perform a thorough clinical examination before thiouracil therapy is instituted and to reexamine the patient at intervals of at least one to two weeks during the first six weeks. Supplemental vitamin therapy, sedatives and other forms of symptomatic treatment have been used in conjunction with thiouracil.

(*a*) Dosage: The first few thyrotoxic patients who were treated with thiouracil received about 1 Gm. daily, but such a dose is now regarded as unnecessarily large; rarely is more than 0.6 Gm. used. The beginning dosage is usually 0.4 to 0.6 Gm. daily; after two weeks it is 0.3 or 0.4 Gm. daily; after a normal basal metabolic rate is obtained it is 0.2 or 0.3 Gm., and after a total of about two months of thiouracil therapy only 0.1 or 0.2 Gm. daily is given. The drug is generally administered in tablet form, each tablet weighing 0.1 Gm. From the point of view of ideal therapeutic effectiveness it would seem that thiouracil should be administered every three hours, day and night, but such a regimen is inconvenient and is not a necessity. In fact, a satisfactory response is obtained if no more than three doses per day are given.

(*b*) Clinical Response: Within one week of thiouracil therapy the patient usually notices improvement, but the changes are more striking during the second, third and fourth weeks. After five or six weeks few, if any, symptoms or signs of thyrotoxicity persist. The tremor, cutaneous changes, tachycardia, palpitation, dyspnea and diarrhea usually will have disappeared; nervousness and the appetite will have decreased, and gain in weight almost invariably will have occurred. The menses tend to improve gradually. Exophthalmos of the nonmalignant type usually shows marked improvement or disappearance during the first few weeks of treatment, but the malignant type often increases in severity. During the first six weeks of therapy the thyroid gland generally does not change appreciably in size or consistency; in some patients it becomes firmer and larger; in some it gets smaller and softer, and in others there is no change. Rarely, a patient complains of pain in the thyroid region.

The basal metabolic rate shows a progressive fall from week to week until a normal level is reached in two to seven weeks, averaging about five weeks. When thiouracil therapy has been immediately preceded by iodide treatment for six weeks or longer the response in the clinical status and in the basal metabolic rate tends to be much slower than when no iodide has been given.

The blood cholesterol [51] usually returns to normal or above normal.

48. Williams, R. H., and Clute, H. M.: Thiouracil in the Treatment of Thyrotoxicosis, J. A. M. A., to be published.

49. (*a*) Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil, J. A. M. A. **122**:78 (May 8) 1943. (*b*) Himsworth, H. P.: Thyrotoxicosis Treated with Thiourea, Lancet **2**:465 (Oct. 16) 1943. (*c*) Newcomb, P. B., and Deane, E. W.: Thiourea Causing Granulopenia and Thrombopenia, ibid. **1**:179 (Feb. 5) 1944.

50. (*a*) Astwood.[49a] (*b*) Williams.[39c] (*c*) Palmer, V.: Hyperthyroidism and Thiouracil, Bull. School M. Univ. Maryland **28**:125 (Jan.) 1944. (*d*) Rawson, R. W.; Evans, R. D.; Means, J. H.; Peacock, W. D.; Lerman, J., and Cortell, R. E.: Action of Thiouracil upon the Thyroid Gland in Graves' Disease, J. Clin. Endocrinol. **4**:1 (Jan.) 1944. (*e*) Astwood, E. B.: Medical Treatment of Hyperthyroidism, Bull. New England M. Center **6**:1 (Feb.) 1944. (*f*) Newman, E. V.; Rienhoff, W. F., and Rich, A. R.: Symposium on the Use of Thiouracil in Hyperthyroidism, Bull. Johns Hopkins Hosp. **74**:152 (Feb.) 1944. (*g*) Gabrilove, J. L., and Kert, M. J.: Sensitivity to Thiouracil, J. A. M. A. **124**:504 (Feb. 19) 1944. (*h*) Friedmann, I.: Thiouracil for Hyperthyroidism, Brit. M. J. **1**:446 (March 25) 1944. (*i*) Welshman, B. C.: Effect of Thiouracil on White Cells, Lancet **1**:195 (Feb. 5) 1944. (*j*) Sloan, M. H., and Shorr, E.: Metabolic Effects of Thiouracil in Graves' Disease, Science **99**:305 (April 14) 1944. (*k*) Bartels, E. C.: Thiouracil in Severe Hyperthyroidism, J. A. M. A. **125**:24 (May 6) 1944. (*l*) Williams and Clute.[37] (*m*) Watson and Wilcox.[38b] (*n*) McGregor, J. K.: Thiouracil and Its Effects on Hyperthyroidism, Canad. M. A. J. **51**:37 (July) 1944. (*o*) Martin, E.: Thiouracil in the Treatment of Hyperthyroidism, ibid. **51**:39 (July) 1944. (*p*) My comments on the clinical results are based on observations made on 174 patients treated by my co-workers and me as well as about 130 cases reported by others. Some reports do not present much clinical data regarding the patients treated, because the main interest was in giving the results of special studies or in reporting toxic reactions to thiouracil.

51. (*a*) Astwood.[49a] (*b*) Palmer.[50c] (*c*) Watson and Wilcox.[38b]

The clinical remission and the normal basal metabolic rate can be maintained, apparently, as long as thiouracil therapy is employed. If therapy is discontinued after a few weeks a relapse of the disease generally appears within two to four weeks. Some patients have been treated continuously [48] for sixteen months. After several months of therapy the thyroid gland tends to show a distinct decrease in size; some glands that were three times normal size at the beginning of treatment decreased to about one and one-half times normal size.

In a few cases, after treatment had been given for six months to a year, it was discontinued, but the condition remained in remission for more than three months.[52]

Thiouracil has been used [53] often only in preparation of patients for thyroidectomy. In fact, Bartels [50k] has used it only preoperatively and in cases of severe involvement. It causes a complete remission of the disease preoperatively in a distinctly greater proportion of cases than iodide therapy does. However, in some patients treated with thiouracil the gland bleeds more readily. Perithyroiditis, which is occasionally associated with thiouracil treatment, adds to the technical difficulties. Iodide therapy used in conjunction with thiouracil probably lessens the surgical difficulties to some extent.[48]

Patients treated preoperatively with thiouracil alone have less cardiorespiratory distress during thyroidectomy than do patients treated with iodide. Furthermore, the postoperative course is smoother; the patient remains quieter and has less fever and tachycardia. The number of two stage operations has been greatly reduced by the use of thiouracil. The incidence of recurrence or of persistence of thyrotoxicosis following subtotal thyroidectomy and the frequency of myxedema have not been determined. Thiouracil has caused a marked decrease in the period of hospitalization.

Toxic reactions to thiouracil have been encountered in approximately 10 per cent of the patients. Most of the complications have appeared in the first five weeks of treatment. These have consisted of fever, morbilliform rash, urticaria, arthritis, vomiting, diarrhea, enlargement of the submaxillary salivary glands, edema of the legs, lymphadenopathy, leukopenia and agranulocytosis. The last of these is the only serious toxic reaction. Only 2 cases of definite agranulocytosis have been reported [54] thus far, although there have been several instances of extreme leukopenia.[55] Both of the patients with agranulocytosis recovered after a rather stormy course. Aside from agranulocytosis, the complications disappear rapidly on discontinuation of thiouracil therapy. In fact, except for fever, arthritis and leukopenia, the complications have been observed to disappear with only a reduction in the size of the dose. When thiouracil therapy is discontinued, iodinization is usually substituted. Two patients who had a febrile reaction to thiouracil had an immediate febrile reaction when thiourea was substituted.[21] Indeed, in 1 patient treated with thiourea alone leukopenia and thrombopenic purpura developed.[40c]

(*c*) Special Clinical Studies: The protein-bound iodine of the plasma returns to normal with thiouracil therapy, reaching this level before the basal metabolic rate is restored to normal.[48]

Sloan and Shorr [50j] found that the administration of thiouracil therapy to a thyrotoxic patient caused a decrease in the excretion of creatine, an increase in creatine tolerance, and a retention of nitrogen, phosphorus and calcium. In a few patients receiving large doses (1 Gm. daily) of thiouracil, hypernatremia, hyperchloremia and a decrease in the carbon dioxide–combining power of the plasma were demonstrated.[56] In some patients without thyroid disease thiouracil promoted retention of sodium chloride, nitrogen, creatinine and creatine. The total serum protein and the dextrose-insulin tolerance were not affected by thiouracil treatment.

The thyroid tissue removed from thyrotoxic patients treated with thiouracil is firm and somewhat rubbery. Occasionally, fibrous tags hang from the capsule. A cut section of the gland generally shows little colloid. On microscopic examination [57] a varied appearance is observed. Commonly the sections show very tall columnar epithelial cells, many papillary projections and little if any colloid. In some areas there are, apparently, solid sheets of cells, and the acinar structure is difficult to discern. Lymph follicles

52. (*a*) Astwood.[50e] (*b*) Williams and Clute.[48]

53. (*a*) Newman, Rienhoff and Rich.[50f] (*b*) Rawson, Evans, Means, Peacock, Lerman and Cortell.[50d] (*c*) Bartels.[50k]

54. (*a*) Astwood.[49a] (*b*) Williams and Clute.[37]

55. I know of several other cases that have not been reported, but the important point is how frequently this complication occurs. Some of the reports on thiouracil have been made only because of the complications encountered. This is apt to be misleading in the determination of the frequency of complications. Of 174 patients whom I have treated, 2 have had agranulocytosis.

56. Williams, R. H.; Bissell, G. W.; Jandorf, B. J., and Peters, J. B.: Some Metabolic Effects of Thiouracil with Particular Consideration of Adrenal Functions, J. Clin. Endocrinol. **4**:58 (Feb.) 1944.

57. (*a*) Rawson and others.[50d] (*b*) Williams and Clute.[48]

are seen in increased numbers. Other sections show less hyperplasia but more colloid. Thus the appearance is that of noniodized toxic goiter, except for a tendency toward more hyperplasia and less colloid. A comparison of sections of the thyroid gland before and after thiouracil therapy shows an increase in hyperplasia in some patients.

Little radioactive iodine is stored by the thyroid gland of a person treated with thiouracil.[50d] The thyroxin content tends to be extremely small,[37] and bioassays of the calorigenic action of these glands reveal little or no activity.[50d] Although the manufacture of thyroxin is in some manner inhibited by thiouracil, the drug does not interfere with the breakdown of thyroxin in normal persons,[37] nor does it interfere with the calorigenic action of thyroxin in myxedematous patients.[39]

The amount of thiouracil present in the thyroid glands of thyrotoxic patients is found to vary a great deal.[48] No correlation has been made between the concentration of the drug in the gland and the response of the thyrotoxicity.

## COMMENT

Many of the antithyroid substances discussed in the previous sections have been of great aid in illustrating the integrative nature of the pituitary–thyroid–body cell relationships as well as in leading to a better understanding of the intrinsic physiology of each unit. The only antithyroid substances that have been given much consideration clinically are iodine and thiouracil. Although many of the claims for iodide therapy remain in dispute, there is general agreement as to its major effects. The effectiveness of radioactive iodine in the treatment of thyrotoxicosis remains an unsettled question. The principle involved in this therapy is the same as the administration of roentgenotherapy to the thyroid, but it has the advantage over the latter in that the irradiation is applied more directly and uniformly, because of the thyroid's capacity to concentrate this iodine readily. The main difficulty encountered with this form of therapy has been in ascertaining the optimum dosage—too much will cause myxedema, and too little will produce only slight or transient effects on the hyperthyroidism.

Indications are that thiouracil is superior to any other form of therapy utilized thus far in producing and maintaining a remission of thyrotoxicosis. Early fears of the goitrogenic effects of thiouracil seriously handicapping its use are no longer justified. Whereas it sometimes causes further enlargement of the thyroid gland, for the most part a reduction in size results after prolonged therapy. Although the technical difficulties of thyroidectomy are greater in some cases in which the patients are prepared with thiouracil than in comparable ones in which they are prepared with iodide, these are reduced by using iodide or desiccated thyroid in conjunction with thiouracil. It is too early to state how extensively thiouracil therapy should be used to the exclusion of subtotal thyroidectomy. It appears that except in a few cases in which there are toxic reactions to thiouracil, the drug can be used indefinitely and that as long as it is used a remission of the disease is maintained. Data are much too meager to state what the ideal period of treatment should be in effecting a "medical cure." Indeed, the obscurity of the primary cause of the disease makes it difficult to know what the ultimate goal in treatment should be, other than to abolish the obvious manifestations of the disease.

The results of studies presented in previous sections indicate that the effectiveness of thiouracil in the treatment of thyrotoxicosis is due to its inhibition of the manufacture of the thyroid hormone. The hormone already manufactured will in time become broken down, and a remission of the thyrotoxicosis will then ensue, but the evidence suggests that the pituitary may become even more active, and as a result hyperplasia of the thyroid gland persists or actually increases. Therefore, the setting appears to be such that on cessation of therapy the thyroid gland would manufacture more hormone than ever. However, since in a few patients thyrotoxicosis has been shown to remain in a remission for several months after discontinuance of thiouracil therapy, certain changes must take place under the influence of thiouracil in the pituitary or thyroid or some other portion of the body which interfere with the manufacture or stability of the hormones or with the capacity of the end organs to respond.

The outstanding handicap to thiouracil therapy has been its toxic reactions. Whereas the only really serious one reported thus far has been agranulocytosis, which has occurred in only 1 per cent of the cases, this complication has such a bad prognosis that the merits of any drug producing it must clearly be greater than other forms of treatment in order to justify its continued use. Not enough data have been accumulated to decide this question accurately. In the meantime, it seems probable that with the precipitously rising tide of interest in this line of investigation either a substance related to thiouracil or perhaps one of an entirely different basic structure with undisputed therapeutic superiority will evolve, as has been the story with the antibacterial drugs.

# Book Reviews

**Practice of Medicine.** Fourth Edition. By Jonathan C. Meakins, M.D., Professor of Medicine and Director of the Department of Medicine, McGill University. Price, $10. Pp. xviii + 1,444, with 517 illustrations, including 48 in color. St. Louis: C. V. Mosby Company, 1944.

A textbook of medicine only eight years old and in its fourth edition is on its record a remarkably vigorous youngster. The ARCHIVES has already reviewed the first two editions (ARCH. INT. MED. **60**:176 [July] 1937; **64**:659 [Sept.] 1939). Both reviews were complimentary and said about all that can be said of the fourth edition. The first review welcomed the new book, liked its British flavor and admired its author for his energy, his skilful planning, his facility in writing with clarity and simplicity and his broad understanding and knowledge of disease. The review of the second edition was equally commendatory. The fourth edition hews to the same line. It is an up-to-date model made on the original last. No doubt it will prove as successful as its predecessors.

**The Diseases of the Endocrine Glands.** By Hermann Zondek. Translated by Carl Prausnitz Giles. Price, $11. Pp. 496, with 180 illustrations. Baltimore: Williams & Wilkins Company, 1944.

The reviewer made a note on the previous edition of this book (ARCHIVES OF INTERNAL MEDICINE, vol. **57**: 239, 1936), and he finds that the comments made then apply pretty well to the present edition. A large amount of interesting material is assembled, and the views of such an authority as Dr. Zondek are of the greatest importance. Some of the comments, however, about the nature of disease are a little confusing, such as the statement (page 131), "It is an axiom of Clinical Pathology that every disease carries within it the germ of recovery." There are many excellent illustrations as well as tables and diagrams and a comprehensive bibliography.

This book is full of interest for the postgraduate and for the specialist who wishes to compare his own ideas with those of an outstanding authority.

**Malaria: Its Diagnosis, Treatment and Prophylaxis.** By William Newbold Bispham, M.D. Price, $3.50. Pp. 197, with 5 plates. Baltimore: Williams & Wilkins Company, 1944.

This excellent description of malaria follows the classic lines of discussion of history, geography, the parasite, the mosquito, epidemiology, symptoms, therapy, etc. Indeed the division of pernicious fevers into various forms (tetanic, hemiplegic, choleraic, algid, cardialgic, bilious, etc.) takes one back to nineteenth century medical writing. The chapters on immunity and animal experimentation are highly instructive; it is unfortunate that so much of the recent work on malaria is still not to be published for military reasons. This book represents, however, an admirable summary of the subject, and the fact that much of the material was reviewed by special experts adds a note of authorty to all that is said.

# News and Comment

**The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.**—Last year twenty-seven applications for grants were received by the trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, nineteen of which were from the United States and eight from five different countries in Europe, Asia and South America. In the twenty-one years of its existence the Foundation has made five hundred and eight grants, which have been distributed to scientists throughout the world. The maximum grant is usually $500.

In the allotment of grants, for the present, researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery. Grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances.

Applications for grants to be held during the year 1945-1946 must be in the hands of the executive committee before April 1945. Letters asking for aid must state definitely the qualifications of the investigator, include an accurate description of the research and state the size of the grant requested and the specific use of the money to be expended. Applicants are requested to state whether or not they have approached other foundations for financial assistance and to include letters of recommendation from the directors of the departments in which the work is to be done.

Applications should be sent to Dr. Joseph C. Aub, Massachusetts General Hospital, Fruit Street, Boston 14.

## CORRECTION

In the article "Hematologic and Genetic Study of the Transmission of Thalassemia (Cooley's Anemia; Mediterranean Anemia)," by Drs. William N. Valentine and James V. Neel, in the September issue (ARCH. INT. MED. **74**:185, 1944), "1 per cent" in the twelfth line of the third paragraph in the first column on page 189 should read "one parent."

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